March 1997

University of Toronto

Volume 74, N° 2

Medical Journal

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- Sturge-Weber Syndrome
- Pulmonary Embolism
- Acute Cholecystitis
- Iliac Artery Stenosis
- Clinicopathological Correlation
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Medical Journal

Established in 1923. An Undergraduate Publication.

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Front cover illustration by John Harvey, Department of Biomedical Communications, University of Toronto.

Editorial

We are pleased to present the second edition of the seventy-fourth volume of the *University of Toronto Medical Journal.* Continuing in a long tradition of excellence, the first edition was well received and we would again like to acknowledge all those who helped make it possible.

In this issue, University of Toronto medical students present articles in an array of disciplines. Our feature article on Sturge-Weber Syndrome provides a detailed review of this rare paediatric neurocutaneous disorder, highlighting both its clinical and pathological features. For medical students, residents, and primary care clinicians, articles reviewing a diagnostic approach to pulmonary embolism, management of acute cholecystitis, and ambulatory blood pressure monitoring in hypertension provide current perspectives of these common conditions. Also, an article on the role of Hepatitis C coinfection in HIV represents researchers' growing understanding into the pathophysiology of these infections and provides management recommendations for persons living with HIV/AIDS. Lastly, a fascinating paper on management of iliac artery stenosis provides a fine example of the potential to apply cutting edge technologies to the improvement of patient care.

For the clinical sleuths, our newly introduced Clinicopathological Correlation section appears again with a neurology case that will challenge medical students and neurologists alike. We would like to thank Dr. Warren P. Mason for the Clinical Discussion and Michael S. Pollanen for the Pathological Discussion. For further intrigue, in the Quick Diagnosis section, a number of common complications of AIDS are highlighted.

A special entry in this issue is a summary of the role of the medical-legal autopsy in Ontario, from Dr. B. Porter, the deputy Chief Coroner of Inquests for Ontario. This practical summary details vital knowledge for any practitioner. In News and Views, our editors continue to take the pulse of the University of Toronto medical community, providing perspectives on the recent OMA deal with the Ontario government, drama therapy, and other current developments and happenings affecting today's clinicians, students, and scientists. Also, the computer software editors once again provide a colorful look at the growing potential of computers in medicine, examining the role of multimedia reference books as a developing part of medical education.

Keeping with our commitment to help carry the journal into the 21st century, we encourage all of our readers to visit the UTMJ online at our new Website address: http://icarus.med.utoronto.ca/mjweb/www.mjweb.htm.

Finally, we would like to thank everyone who assisted in making this second edition possible. We would especially like to thank our art directors and the entire Biomedical Communications division as well as our multi-talented support team. As always, we thank all of our patrons and subscribers, for their commitment to medical students at the University of Toronto Faculty of Medicine.

We hope you enjoy this edition of the UTMJ and we look forward to continuing to provide a high quality medical publication in our next issue.

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Is There a Future for Complementary Medicine?

Heather Karn, M.Sc. (9T8)

Unconventional medical practices, or 'alternative remedies' include acupuncture, herbal medicine, chiropractic, and homeopathy. These remedies are commonly used by patients with a wide variety of illnesses. However, the majority are used by people with cancer, arthritis, AIDS, and other ailments that conventional medicine has not treated effectively or cured.[1] Because these treatments are so diverse, it is difficult to make generalizations about their efficacy. Physicians are often divided in their opinions, and debate over alternative therapies can be emotionally charged. Despite the fact that the medical community has reached no consensus about these treatments, their use among patients has continued to increase.[2] Surveys in Canada and the US estimate that 20-30% of the population uses unconventional remedies, spending $10 billion annually.[1] Studies have shown that between 50-80% of all cancer patients use some form of alternative therapy in conjunction with conventional treatments.[1,2] It has been suggested that unconventional medicine addresses

The Double-Edged Sword of Compromise: New Developments in Medical Student Politics

Jeremy Theal, B.Sc. (9T9)

Medical Society VP External Assoc. Jr.

Over the past number of decades, the practice of medicine has changed dramatically. As our level of understanding of the body and disease has increased and new technologies have evolved, patients have developed higher expectations of the services medicine can render. More recently, the profession has been faced with the challenge of performing to these high standards within the confines of an ever-shrinking base of resources. As such, it has become more and more necessary for today's medical students to understand the gravity of the socioeconomic context in which they must practise medicine, and how factors in this environment can have a profound effect on the quality of patient care. Being aware of such issues, medical students have developed increasingly strong ideals and beliefs about how our health care system can best deliver quality care. Accordingly, in recent years we have also become more politically and socially active in order to voice our beliefs to those that make decisions about the health care system. Traditionally, students have had very limited formal input into sociopolitical decision-making processes affecting the health care system; we have had to be content giving our opinions as an "outside group". Over the last year, encouraging developments have taken place which have increased the ability of students to voice their concerns and participate in decision-making in political arenas. However, these increases in collaboration have also brought elements of compromise that must be carefully considered as students continue to develop their role as part of the medico-political system.

What has happened recently to bring about a change in the student political position? An answer to this question requires a short history of recent events. Members of PAIRO (Professional Association of Interns and Residents of Ontario) and the SSOMA (Student Section of the OMA, representing undergraduate medical students) have been working for a number of years to increase the political voice of medical students. They have gradually gained, for example, a number of observer or active member positions at OMA meetings and on OMA committees. However, until recently, students have met with only limited success in exacting true change when working with such groups as the OMA because of their limited participation privileges and role in decision-making in these organizations. In addition, past student attempts to provide direct input into government health care decision-making processes have often proven extremely frustrating. Government has allowed only very limited (if any) participation in deliberations, and has often blatantly disregarded any proposals, which student organizations, such as PAIRO, have put forth.

Last year, the Harris government proposed billing number restrictions in an attempt to solve the persisting problem of physician maldistribution in Ontario. Knowing that billing number restrictions were an unrealistic and ineffective solution to service maldistribution, which would surely endanger

proper patient care in rural communities, in February, 1996 PAIRO launched a campaign called "Dialogue '96". Working directly with members of 65 underserviced communities, the result of this campaign was a document PAIRO entitled "Answering the Call", which contained 49 concrete recommendations as a comprehensive plan to solve physician maldistribution issues in Ontario. Encouragingly, a few of the recommendations in this comprehensive document were accepted for implementation by the government. However, the majority of the plan was disregarded, and the government continued to threaten implementation of billing numbers, which would completely undermine the potential effectiveness of PAIRO's solution as outlined in "Answering the Call".

Later in 1996, OMA/government negotiations involving physician payment issues such as thresholds, clawbacks, and CMPA premiums resulted in the development of a proposed Interim Agreement. Outlined as part of this agreement was the much-dreaded implementation of billing number restrictions. PAIRO and the SSOMA (Student Section of the OMA) mobilized swift and loud protest against this plan. Protests included a "candlelight vigil", where students gathered outside the downtown Toronto conference room where OMA Council was to vote on possible acceptance of the Interim agreement. They stood in complete silence, symbolizing the manner in which the OMA and Government were implementing a plan that drastically affected the lives of medical students and quality of care of patients in underserviced communities, yet these people were not consulted or allowed to participate. The campaign was successful, and the agreement was overturned - here, medical students had undeniably demonstrated that they would not stand for such injustices against their rights or the rights of patients.

As another round of negotiations between the government and the OMA began, medical students were included much more fully in the process. The OMA actively listened to members of SSOMA and PAIRO, and agreed to table the entire PAIRO "Answering the Call" document as part of their negotiating position. Both groups were included in a special "Second Table", which was a group of representatives that worked directly with the OMA negotiating team to plan the details of what the OMA would set as goals of negotiation. In December 1996, a second Interim Agreement was proposed by the Government and the OMA. In this agreement, established doctors were to gain the same monetary benefits of the previous Interim Agreement, but billing number restrictions were replaced with fee discounts for new doctors locating in overserviced areas. Though there were other new positive aspects to this agreement, such as a $50 million dollar program of incentives for those doctors that decided to locate in an underserviced area, medical students were very disturbed with the precedent this agreement was setting. Never in the history of health care in Ontario had there been differential treatment of doctors at different stages of the profession. Regardless of their age or number of years of experience, all Ontario physicians had been regarded and renumerated as equal by the Government. This interim agreement, if accepted, set a precedent of differential treatment that many medical students felt might only be the beginning of many more future infringements on their rights as practising professionals.

As continually promised by the OMA, medical students had extensive representation and opportunity for participation in discussions surrounding the new Interim agreement. The OMA made every effort to include students in meetings and teleconferences with board members and members of the negotiating team. However, student representatives felt somewhat betrayed; even with all this consultation, the one issue they had stood adamantly against had been included in the Interim Agreement. Student representatives were told by the OMA that their wishes had been taken to the table

such psychological needs as hope, sense of control, and independence more effectively than mainstream medicine, thus allowing patients to play an active role in their treatment.[3]

Because patients often perceive ignorance, a lack of interest, or a dismissive attitude towards complementary medicine on the part of their physicians, most do not inform their doctors that they are using these therapies.[1] When asked by patients, physicians often explain that there may be drug interactions between traditional and alternative medicines, and that the safety and efficacy of many of these treatments remains unproven.[4] Although this is certainly true, there is undeniable potential in plant-derived medications and other alternative treatments. For example, there is active pharmacological research investigating phytochemicals and their derivatives such as camptothecin, taxol, taxotere, topotecan, CPT-11, and vinorelbine for use as chemotherapeutic agents. Also, although acupuncture has been used for centuries, it has recently begun to gain acceptance in the mainstream medical community, and it is now widely recognized that more investigation in this area is indicated.[1,5,6]

Unfortunately, barriers exist to finding reliable information about alternative practices. There is a potential for biased information about these treatments from com-

panies who market products or procedures that lack rigorous scientific testing of their value.[4,5] Randomized controlled trials have not been done for most alternative remedies, although in recent years efforts have been made to increase such research in this field. In 1991, the US Congress devoted $2 million to the Office for the Study of Unconventional Medical Practices at the National Institutes of Health (NIH) in Maryland. The primary function of this study will be to determine which alternative therapies are medically effective. A panel of medical experts met in 1992 and agreed that to receive NIH funding, alternative medical practitioners would be required to present data using strict scientific methodology such as double blind randomized trials, and peer review to evaluate scientific worth of data and meta-analyses.[7] Recently, guidelines were created by this group to warn patients about potentially fraudulent alternative remedies. These guidelines included: ensure that treatments have been evaluated in clinical trials; be cautious of practitioners who claim the medical community is trying to keep their alternative cure from the public; ensure that the treatment does not rely exclusively on nutritional or dietary therapy; be wary if the treatment claims to be harmless, painless, or to not produce unpleasant side effects; be on guard if the practitioners claim to have a

during negotiations, but that unless differential treatment of new physicians as a way of solving physician maldistribution was included in the agreement, the government would have terminated negotiations. Students found this very hard to understand - how could the government be so irrational? Both Gerry Rowland, President of the OMA, and David Pattenden, CEO of the OMA, explained that "only a very small part of politics is rational - and the rest is emotion, which has no rational basis". Despite protests based on fundamental principle from PAIRO and the SSOMA, the OMA Board and negotiating team assured the OMA Council that no better agreement would be possible, because the government would not negotiate any further. The Interim Agreement was ratified in January, 1997.

In light of this progression of events, it is interesting to consider what students have gained, and what we have lost. Surely, one thing we have gained is the respect of many members of the medical profession and the political sector - for we never would have been given such opportunities for direct consultation in the past year without this respect. As well, we have gained some measure of input into the health care decision-making processes at hand. Surely we were much less effective before, when we were merely protesters, locked outside the rooms where decisions were being made.

Then why, after gaining all these things, do we still feel somewhat empty, as if we have accomplished less than was, and is, possible? It is because, in my opinion, there is a definite cost to becoming part of the established groups and mechanisms involved in defining our health care system. This cost is a loss of our ability to remain true to our ideals. Medical students are unique in the medical profession because, as a group, we hold very strong morals and ideals, based on our original reasons (still fresh in our minds) for entering medical school. Our attitudes have not been modified or tarnished by the disillusionment that can occur as a result of many years of practice in the status quo "health care system". While some would disregard our idealism on the belief that we are naive or inexperienced, there is no question that our attitudes are founded in the values that are most basic and important to every health care professional. Our voice, when it stands on its own, can help to remind others involved in decision-making processes what values are the most important to consider when making changes to the health care system. When we become part of a larger process, amongst those who are not as idealistic, our message is diluted in the name of political compromise. Certainly, to some degree, compromise is necessary - for example, we accept that as future new doctors, we have to take our share of the "cuts" so that the health care system can afford to provide quality health care for all. However, by being involved with the negotiation process that approved the latest OMA Interim Agreement, we have also compromised our own values on two very important issues. First, we have compromised our own rights by conceding to differential treatment of new physicians. But second, and more importantly, we were forced to compromise the rights of our future patients by accepting government-imposed physician redistribution measures that will degrade the long term quality of health care in rural areas. Moreover, we accepted these measures knowing that other redistribution plans, such as those researched by PAIRO, would have had far better long-term effects on rural care.

Certainly, the greater acceptance and stronger voice students have recently gained in medico-political arenas allows us to play a larger part in decision-making dialogue. In the coming months, however, our objective should be to decide how we can best utilize this newly-increased level of collaboration. We must strive to act in a way that resonates with our desire to maintain not just our own rights as new physicians, but more importantly, the rights of our patients.

Drama Therapy in Paediatric Psychosocial Rehabilitation

Renée Waterman, B.Sc. (9T9)

Drama therapy, less familiar than art, music or dance therapy, has only been practised formally for the past twenty years. Drama was first used for curative purposes in 1945 with the development of a structured use of role play called psychodrama.[1] In the 1950's, the field of child psychotherapy saw the development of the play therapy approach, which used role play and pretend games.[1] It was not until the 1960's, during the development of new humanistic techniques in psychotherapy, that drama therapy programs emerged.[1] The success of these programs within special populations in the United States led to the formation of the National Association for Drama Therapy in 1979.[2] Today, group or individual drama therapy is used in the treatment of children, adolescents, and adults.[2] It is used in hospitals for both acute and chronic care patients, outpatient clinics, prisons, schools, universities, homes for the elderly, and also in personnel management.[2] Drama therapy is particularly useful in a rehabilitation and occupational therapy setting because the techniques can be flexibly adjusted to suit various levels of communication, awareness, and physical ability.[2] Although it is not yet widely used, drama therapy has been found to be a powerful tool using spontaneity and imagination to build self esteem and self confidence, particularly in children.

Drama therapy is defined as the intentional and systematic use of dramatic processes to achieve psychological growth and change.[1] The therapist acts as a facilitator to advance the session from the warm-up phase, to the phase where the client's problematic areas can be explored, and finally to a closure where the work undertaken in the session is reflected upon. Along with its therapeutic use, drama therapy is also becoming appreciated for its diagnostic applications as a powerful indicator of the individual's cognitive style and personality organization.[3] The aims of drama therapy in paediatric psychosocial rehabilitation are to: initiate social interaction, to master release and control of emotions, to examine behaviour and role patterns, to stimulate spontaneity and imagination, and most importantly, to build self esteem and self confidence.[3]

The very nature of drama necessitates social interaction with others, however, role play can protect an individual from experiencing anxiety in social situations.[3] In a scene between two actors four relationships exist: the relationship between the actors, between the characters, and between each character and actor.[3] Because the scene is improvisational, problems in the actor-actor relationship become expressed indirectly and are dealt with at a distance.[3] Drama allows the individual to externalize interpersonal struggles and explore alternative solutions.[4] In a paediatric rehabilitation setting, children have the opportunity to practise communicating their needs through movement, mime, sound, imitation, or dramatic play.[4] Role play and improvisation not only promote listening skills, but also promote the development of trust and group cohesiveness.[4]

Both the release and control of emotion are important to the psychotherapist and the actor, therefore the drama therapist has a two-fold interest in emotional mastery.[5] Children in a rehabilitation setting may experience a great deal of frustration and may need a cathartic release.[6] Adolescents, in particular, achieve a sense of emotional release via creative expression.

'secret formula' that only they have access to.[3]

Here in Ontario, a group of physicians are organizing a section of the Ontario Medical Association devoted to setting standards and locating funding for research into unconventional remedies. This group believes that traditional and alternative therapies can complement each other, and that regulations are needed to ensure the safety of patients who choose to use them. Thus, it seems that here in Canada, the medical community is becoming more open to examining the efficacy of complementary medicine, with the potential for incorporating those treatments deemed truly effective into traditional medical practice.

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Fleming Prize in Neurosurgery

The Division of Neurosurgery at the University of Toronto has awarded the annual Fleming Prize for 1995-1996 to Vikas Tuli (9T6) for his article, "Football cervical spine injuries", which was published in the December 1995 issue of the University of Toronto Medical Journal. The Fleming Prize is awarded annually and the current award for 1996-1997 is still available. The article must be based on work performed by an undergraduate University of Toronto medical student, but the work does not need to have been performed at the University of Toronto. Preference will be given to work published while the author is still an undergraduate student. The award is $250. Any interested University of Toronto medical students should submit an article relating to neurosurgery to the University of Toronto Medical Journal.

Medical Student Research Day Winners

The Undergraduate Medical Student Research Day was held on January 14, 1997. There were 78 abstracts presented and each poster was judged by at least 3 faculty members. Undergraduate students judged to have the best presentations in each of five categories are awarded the George Brown Memorial Awards. The winners for this year were:

Novice Researcher (Basic) Category:
Kunuk Rhee (9T9) for "Heat Stress confers protection against ventilator-induced lung injury", supervised by Art Slutsky, Department of Medicine.

However, it is equally important for adolescents to attain a sense of mastery over their emotions.[6] Acting out unconscious feelings forces the child or adolescent to confront themselves and to discuss the enacted fantasies.[4] Watching others exhibit a range of emotion can help clients identify, imitate, and integrate similar expressions of feeling.[4] Some therapists use the theoretical model of affective, behavioural, and cognitive aspects of emotion to assess the therapeutic needs of the client.[5] The child requiring the affective treatment approach is an emotionally rigid individual whose therapeutic premise would be to express repressed feelings.[5] The therapist may use an approach that decreases emotional distance from the scene by using reality based events and having the individual play herself. The purpose of this approach is to decrease cognitive control over emotional response. The cognitive approach is used for emotionally impulsive children whose therapeutic premise is to develop the necessary cognitive structure to process emotional material without becoming overwhelmed.[5] In this case, the drama therapist may increase emotional distance and cognitive structuring by using fictional events and having the individual play an assumed role or use masks or puppets. Finally, the behavioural approach is used for children who experience the appropriate emotion but suppress its communication.[5] This approach focuses on expressive techniques and improvisations that emphasize acting, rather than thinking or feeling.[5] Combinations of these three methods are also used in an effort to explore emotional struggles.[5]

Contemplating behaviour and role patterns is another important aspect of psychosocial rehabilitation. The sense of permission to be different and to escape in drama can lead to a greater self awareness.[6] Drama provides the opportunity to recreate the image of self, which can be particularly important following physical or emotional trauma.[7] Roles that individuals choose can provide insight into their personality and character.[4] Characteristics of roles and the degree of flexibility in role selection can provide diagnostic cues and evidence of change over time.[4] Roles may seem unalterable because they are part of internalized self representations that allow no change and are reinforced by family and community.[4] Drama therapy has been successful in children with behavioural difficulty because it provides the child with the opportunity to rehearse new behaviour in a protected environment.[4,8]

Another major focus is stimulating the child's creativity and spontaneity.[3] The therapist's interventions are directed at the disruptions in the child's spontaneous play in an attempt to identify inhibitions.[3] Improvisation helps the child develop the ability to adapt to new situations, to accept change and transition, and to trust one's own capacities.[3] By developing imagination and a sense of humour, the child will gain perspective to see beyond the present reality. This perspective will allow the child to discover options and the ability to transform.[3]

Many physically and developmentally disabled children and adolescents are quite aware that they are different. As a result, low self esteem is common in these populations.[7] Having the freedom and chance to express oneself in a non-judgmental way can increase self esteem by providing an opportunity to experience oneself in a new way.[7] Drama does not focus on intellectual or physical exercises but more on self presentation and emotion.[7] The group process allows the clients to feel less alone in the process of growth and to learn from one another's successes and failures.[7] Children can improve their own self esteem by seeing how they can help others.[7] Drama provides endless opportunities for winning and succeed-

ing and is geared toward eliciting individual strength. This therapy has been successful in increasing extroversion scores and communication in the treatment of severe shyness.[9] It has also been found to be successful in increasing self esteem, decreasing depression, and decreasing psychological symptoms in adolescent girls who have been sexually abused.[10]

Currently, drama therapy does not refer to a specific theory or technique generated by one person.[2] Techniques in drama therapy are used without any firm theoretical basis.[2] This lack of theoretical framework is partially due to the fact that many drama therapists, are antitheoretical and because research in this field is problematic.[11] Although the temptation to quantify and to achieve academic respectability as a mental health clinician is great, this field is both an art and a social science that is concerned with nonobservable phenomena.[11] Empirical research in drama therapy is problematic in design, in randomizing subjects, in establishing validity and reliability, and in finding appropriate measures for analysis.[11] Qualitative approaches to analyze thought, feeling, creative processes, and insight would be the most verifiable.[11]

Drama therapy has been successful in paediatric psychosocial rehabilitation for several reasons. Drama offers the possibility of externalizing emotion and learning from the experience. Drama therapy involves improvisation, which permits an intimate psychological look at others. Drama encourages the expression of strong positive and negative emotions. Finally, drama promotes the expression of verbal and nonverbal modes of thinking.[1] It works for children because there is a developmental thrust to this process - children use dramatic play spontaneously.[1] This therapy works for adolescents because they have physical, sexual, emotional, and social tensions.[6] Drama gives adolescents an opportunity to experiment with future roles with safety and distance where they are exempt from real life consequences.[6] Because it is a profession that spans both creative and mental health disciplines, drama therapy offers great potential for further research into the nature of interpersonal processes.

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Novice Researcher (Clinical) Category:
Lisa Hicks (9T9) for "Clerkship training and medical student attitudes regarding effective collaboration with community agencies", supervised by Don Wasylenki, Department of Psychiatry.

Experience Researcher (Basic) Category:
Jeff Hall (9T8) for "MR volumetry of frontal lobe regions in Alzheimer's patients: an effect of sex?", supervised by Sandra Black, Department of Medicine.

Experience Researcher (Clinical) Category:
Kate Cochrane (9T9) for "Clinical rating scales in the emergency assessment of suicidal risk", supervised by Jodi Lofchy, Department of Psychiatry.

MD/PhD Student Researcher (Basic or Clinical) Category:
Louis-martin Boucher for "Binding sites of cytoplasmic effectors TRAF 1, 2 and 3 on CD30 and other members of the TNF receptor specificity", supervised by Tak Mak, Department of Medical Biophysics.

Louis-martin Boucher and Lisa Hicks will be given financial support to present their work at the 37th Annual National Student Research Forum at the University of Texas, Medical Branch at Galveston. Each year, the Department of Medicine sponsors one student researcher to attend the Forum. This year the winner of the sponsorship is Kunuk Rhee.

The 1996 Gairdner Foundation International Awards

Anna Mason B.Sc. (9T9)

Every year since 1959, The Gairdner Foundation has given awards to leading medical scientists from many countries. The foundation was established by James A. Gairdner who believed that the achievements of medical scientists should be recognized in a meaningful way. James Gairdner was born in Toronto in 1893 and became a good scholar and an exceptional track and field athlete. After serving in France during World War I with the Canadian army, Gairdner retired with the rank of Major. Soon after, he became a successful stockbroker and industrialist, respected by his peers for his ingenuity. James A. Gairdner decided to take up oil painting after a severe attack of arthritis at age 56 and subsequently exhibited his paintings at Mount Allison University. Later, the university conferred upon him an honorary Doctor of Laws degree. James A. Gairdner always showed a practical interest in medical research and clinical medicine which led him to establish his foundation to recognize the front-runners in medical science.

The purpose of the Gairdner Awards is to recognize individual scientists whose outstanding discoveries or contributions constitute tangible achievement in the field of medical science. The $30,000 awards are not intended as grants to support future research and the winners are free to use the funds as they wish. Since 1959, 243 scientists have been honoured with a Gairdner Foundation Award, 46 of whom have later won a Nobel Prize.

Pharmacological Treatment of Alzheimer's Disease

Alice Ordean, B.Sc. (9T8)

Alzheimer's disease (AD) is an insidious and progressive neurologic disorder characterized by memory loss and other cognitive impairments including aphasia, apraxia, agnosia, and disturbances in executive functioning.[1] AD is currently the most common cause of dementia in the elderly, accounting for more than half of all cases.[2] The prevalence of AD is a function of age; before age 65, the prevalence is approximately 1-2% and this increases to 10% after age 85.[2] With such a large proportion of the elderly affected by this illness, pharmacological treatment of AD is certainly of great interest.

The finding of a gross deficit in central cholinergic transmission in AD led to pharmacological research into cholinergic agents as potential medications for this disease. This cholinergic hypothesis is based on evidence of loss of choline acetyltransferase, the enzyme responsible for the synthesis of acetylcholine, in post-mortem brains of AD patients.[4] This in turn gave rise to the concept of restoring acetylcholine levels to normal to improve symptoms.

Tacrine (tetrahydroaminoacridine) is a cholinesterase inhibitor that was the first drug to be approved for the treatment of AD. To date, it has been the only treatment that consistently shows a benefit in double blind placebo controlled clinical trials, producing a significant improvement in approximately 40% of patients.[5] Tacrine is rapidly absorbed from the gastrointestinal tract and excreted primarily by the kidney, with an elimination half life of three hours. Serum tacrine concentrations predict the risk of adverse reactions. Liver enzyme activity increases in approximately 30% of all patients treated, indicating a potential for increased risk of liver damage/failure. Recently, a positive correlation was demonstrated between both memory and cognitive improvement and plasma tacrine concentration.[3]

Another drug of this class with central cholinergic activity is velnacrine. A multicentre investigation showed a clinical improvement in about 30% of AD patients taking the medication, which, although promising, is not considered sufficient to compare it to tacrine.[3] A third cholinesterase inhibitor, eptastigmine (heptylphysostigmine), is a physostigmine derivative with low toxicity and long lasting inhibitory effects.[6] This drug is rapidly distributed in tissues and readily enters the central nervous system. Furthermore, it can be expected to effectively inhibit acetylcholinesterase in the brain over a prolonged period of time.[7]

Another group of drugs with potential for use in the treatment of AD are nootropic agents, which have positive effects on organically impaired cognition and nervous system function.[8] This class of agents includes oxiracetam, pramiracetam and aniracetam. Of these agents, oxiracetam has been proven to penetrate the central nervous system and enhance various neuropsychological functions in different types of mental decline in the elderly.[9] Pramiracetam has also been shown to access the central nervous system of AD patients, but did not confer any symptomatic benefits.[9] The last agent in this group, aniracetam, has not yet been proven to enter the systemic circulation after oral administration.[9] Currently, the nootropics show only marginal efficacy and further research is needed to examine the benefit of these agents.

The cholinergic loss of AD results from the degeneration of subcortical neurons in the basal nucleus of Meynert, which project to the cortex and hippocampus. Restorative therapy differs from neurotransmitter replacement, since its goal is to enhance the survival and function of neurons vulnerable to degeneration.[10] Neurotrophic medications offer the possibility of slowing down this neuronal degeneration. Selegiline (deprenyl) is an irreversible

monoamine oxidase B inhibitor which also inhibits the uptake of catecholamines by neurons and increases the turnover rate of dopamine (by blocking presynaptic receptors). These effects work to retard the progress of neurodegeneration in dementing illness.[9] Acetyl L-carnitine (ST200), synthesized from L-carnitine by carnitine acetyl transferase, is another neuroprotective agent.[9] This drug has been shown to improve the cognitive performance of patients suffering from Alzheimer's-type dementia.[11] Several studies have concluded that intravenous and oral administration of ST200 can lead to its accumulation in the plasma and cerebrospinal fluid of patients with AD.[9] Gangliosides (GM1) are normal components of mammalian cell plasma membranes and have been found to have neurotrophic properties. These agents can be administered by intravenous or intramuscular routes, the latter route permitting a longer half life. Exogenous administration of gangliosides appears to be protective against mechanical and/or biochemical injury of nerve tissue and helps repair functions in both the central and peripheral nervous systems.[12]

Other pathologic processes in AD involve the abnormal deposition of beta amyloid in the brain and the presence of neurofibrillary tangles. New strategies are evolving based on limiting amyloid deposition, increasing its removal or protecting the neurons from its possible neurotoxicity. For example, anti-inflammatory compounds such as indomethacin have been linked to the production of amyloid. Pharmacological treatments based on this concept, if started early enough, might prevent neuronal degeneration and the evolution of clinical dementia. Another area of research involves the study of neurofibrillary tangles, which result from the aberrant processing of a protein called "tau". Treatment aimed at decreasing tau's abnormal phosphorylation may help to conserve normal neuronal function.[5]

As current treatments for AD are focused on correcting neurotransmitter deficiencies (in the hope of stabilizing or improving symptoms) and not on retardation of the underlying pathologic process, the neurotrophic agents with their potential to stop or even reverse neuronal degeneration are of extreme interest. To date, there are few treatment options that improve cognition in Alzheimer's disease. There is much optimism for the future with the development of restorative, protective and preventive strategies. The pace of research into alternative pharmacological treatments is quickening and new investigations will yield additional drugs with the hope of ending the personal tragedy of progressive dementia and the emotional distress of many families.

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On October 25, 1996 the Gairdner Foundation International Awards were presented at the National Club in Toronto. Robert S. Langer is the Kenneth J. Germeshausen Professor of Chemical and Biomedical Engineering at the Massachusetts Institute of Technology. His Award is in recognition of his development of synthetic polymer methods that allow the slow release of drugs. Dr. Langer's work has revolutionized drug delivery in a variety of diseases and has resulted in new therapeutic modalities. Barry J. Marshall is an Associate Professor in the Department of Internal Medicine at the University of Virginia. His Award is for the discovery of the role of *Helicobacter pylori* as a cause of peptic ulcer disease. His discovery has led to a major change in the way that ulcers are treated, specifically by the use of antibiotics and other drugs to control the bacterial infection. Janet D. Rowley is the Blum-Riese Distinguished Service Professor in the Department of Medicine at the University of Chicago. Her Award is for establishing the critical importance of chromosomal rearrangement as a specific cause of human cancer. She is also recognized for her lifetime of research to identify the genes that are rearranged to cause leukemia and lymphoma. James. E. Rothman is Vice-Chairman, Sloan-Kettering Institute, and Chairman of the Cellular Biochemistry and Biophysics Program at the Memorial Sloan-Kettering Cancer Center in New York; Randy W. Schekman is a professor in the Department of Molecular and Cell Biology and an Investigator in the Howard Hughes Medical Institute at the University of California, Berkeley. These two scientists are honoured jointly for their

independent work on the identification of proteins involved in intracellular traffic and vesicle fusion. Recently, others have shown that the same proteins are essential for neuronal communication and thus, this research has led to a new understanding of brain function and disease.

The Gairdner Foundation hopes that these awards will focus public, professional and scientific attention upon significant achievements in the medical field and will contribute to improved communication of ideas among scientists.

The 1997 Gairdner Foundation Awards Lectures will be held on Friday, October 24, in the McLoed Auditorium in the Medical Sciences Building, at the University of Toronto.

Thanks to Dr. Harry Schachter for kindly providing this information.

PAPNET and CytoBase: strategies to improve cervical cancer screening in Ontario

Karen Gronau, M.Sc. (9T8)

Despite the fact that it is a preventable disease, cervical cancer continues to be a major cause of cancer deaths in women, with more than 150 deaths in Ontario each year. Because it develops slowly, diagnosis at an early stage is essential. Although the Pap test is widely available, one third of all women fail to have the test regularly. The test is still performed manually, and requires a technician to search through the more than 300,000 cells on each slide. Because abnormal cells are often small and difficult to detect, up to one fifth of tests with an abnormality can be reported as negative. Unfortunately, the obligatory

The New Drug Cocktails: Is AIDS Research Finally Getting Somewhere?

Brian Rotenberg, B.Sc. (0T0)

AIDS is again prominent in the mainstream press since Dr. David Ho, of the Aaron Diamond AIDS Research Center in New York City, was named Time Magazine's Man of the Year for his pioneering work on the latency period of HIV. His team's work is actually the latest in a series of developments against this disease that may be pointing in the direction of eventual successful treatment. With the latest statistic from the United Nations AIDS Program stating that 22.6 million people worldwide are infected with the virus, and the knowledge that this number is still growing rapidly, such work is certainly timely.[1]

Most treatments for AIDS are based on blocking a step in the replication cycle of HIV, a retrovirus composed of two strands of RNA and several enzymes packaged together in a protein capsule. When the virus encounters a host CD4 T-cell, special proteins on the viral coat bind to the CD4 receptor and its co-receptor on the T-cell membrane. The retroviral RNA then enters the cell and the viral reverse transcriptase converts the RNA to DNA. Integrase, a second viral enzyme, then incorporates the viral DNA into the host cell's genome. At this point, the virus begins to use the host cell's protein synthesis machinery to create millions of copies of both viral RNA and viral capsule proteins. Viral proteases then cut the lengthy viral proteins into the smaller subunits of the protein capsule. New copies of the virus assemble, the T-cell is lysed, and millions of new viruses are released into the bloodstream to begin the life cycle anew.

Much excitement has been generated of late by the application of multi-drug 'cocktails' as a protocol for AIDS treatment. The premise of this therapy is that if a drug blocks one step in the life cycle of HIV, the virus may adapt to the drug and overcome the blockade, but if several drugs are used simultaneously to block multiple steps in the life cycle, adaptation is less likely. The latest prescription for cocktail therapy includes the reverse transcriptase inhibitor AZT (azidiothymidine), the related drug 3TC (lamivudine), and Invirase (saquinavir), one of the new class of drugs known as protease inhibitors.[2] By blocking both the conversion of RNA to DNA, and the formation of capsule proteins, researchers have met with amazing success in treating AIDS patients in the early stages of infection.[3] A recent multicentre, double-blind, randomized, placebo-controlled trial, investigating both drug tolerance and drug combinations, demonstrated significant reductions in circulatory viral load levels in patients on the combination therapy as compared to those on single drug therapy.[2,3] Although these trials are recent and are not yet officially completed, the potential therapeutic value of these medication combinations seems extremely promising.

It was previously believed that HIV lies dormant in the body for an indeterminate period of time after infection before becoming active in response to some unknown factor. Research has now shown that the battle begins from the moment of infection and takes place in the lymph nodes, which are unfortunately more difficult to study.[1] Eventually the body exhausts the immunologic reserves in the lymph nodes, and at that point the virus is released into the circulation and the viral load in the blood spikes. With the advent of multi-drug cocktail therapy, researchers hope to effectively supplement the efforts of the body to eradicate the

virus from the lymphatic system early in the course of the disease, thus leaving more immune system capability available to deal with virus not destroyed by the drugs.

Another dramatic development in the fight against AIDS, in the field of molecular biology, came last summer when researchers discovered that certain people have an inborn genetic resistance to HIV. As mentioned above, HIV uses the CD4 receptor and its co-receptor to gain access to the CD4 T-cell. This co-receptor, a chemokine known as CKR-5 or CCR-5, is involved in the presentation of the virus to CD4. In a population of several men who had never seroconverted despite repeated contacts with HIV, researchers found that all carried two defective copies of the CKR-5 gene in their genome. Since their T-cells did not possess functional copies of the co-receptor, HIV could not gain access to their T-cells.[4] As Dr. Flossie Wong-Staal, a leader in the gene-therapy approach to treating AIDS, suggests, "If it's [CKR-5] dispensable for a person but not for the virus, then it's a terrific finding. You could create a mutant copy of CKR-5 or inhibit its expression or use chemicals to inactivate it".[5]

A few other protease inhibitors are currently being produced for use in cocktail therapy; Crixivan (indinavir sulfate) and Navir (ritonavir) have recently been approved by the FDA. Integrase inhibitors, which may be capable of blocking yet another step in the life cycle of HIV, are also under development.[6] Finally, the bi-allelic mutations in the CKR-5 gene that seem to confer HIV resistance certainly deserve further investigation. However, these new pharmacotherapies notwithstanding, it must not be forgotten that although AIDS is certainly a prevalent and terrible disease, it is also eminently preventable. In fact, the majority of new infections result from unprotected sexual activity, needle sharing among intravenous drug users, and tainted blood transfusions, all of which can certainly be avoided. Only by using information and education to increase public awareness around these issues will it be possible to turn the tide against HIV in terms of decreasing the infection rate. Unfortunately, in underdeveloped countries where rates of infection are still increasing rapidly, it will be very difficult to increase public awareness about HIV risk factors. Further, since in these countries the general populace cannot afford medical care, cost effectiveness of drug administration must also be a major concern when developing new therapies. Only when a balance is struck between increased public education producing a change in risk behaviours and new medications improving the outcome of those infected, will there truly be the potential to conquer AIDS.

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quality controls in place only require 10% of negative results to be re-screened, thus allowing false negatives to go unrecognized. The PAPNET system (from Excel Bestview Medical Labs) is able to address the inherent problems of manual screening of pap tests. It utilizes advanced neural network technology to re-screen 100% of cervical cells on pap smear slides, and thus is capable of finding even very few abnormal cells (as few as 12 per slide). Combined with manual screening, PAPNET produces a statistical false negative rate of 0.1%, thus significantly improving the diagnostic accuracy of the Pap test.

More than 2 million Pap tests are performed annually in Ontario. Women often have tests performed at different laboratories from year to year. Because of this, pathologists are unable to access patients' previous tests in order to assess changes over time. As cervical cancer develops slowly, this is essential. To address this problem, six labs responsible for reading 60% of the province's Pap tests, have recently created a new company called Inscyte Corporation to compile all Pap records produced in these companies' labs. Inscyte is working with the Ontario Cancer Treatment and Research Foundation, with the goal to reduce the number of women diagnosed with and dying from cervical cancer in Ontario by half by the year 2000. Test results are stored in CytoBase, an artificial intelligence database. Thus, each patient's longitudinal Pap smear record will be available, and the system can also automatically alert pathologists when patients should have another smear performed. Inscyte's ultimate goal is that all of Ontario's cytology labs will eventually be a part of this system. The database has both clinical and epidemiological research potential, and may also serve as a prototype for other medical record repositories.

More Than Just Skin-Deep: A Review Of The Sturge-Weber Syndrome

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JOHN HARVEY

Introduction

Sturge-Weber syndrome (SWS) is a neurocutaneous syndrome characterized by leptomeningeal angiomatosis with or without a facial port-wine stain or nevus flammeus, associated with ipsilateral gyriform intracranial calcifications and cerebral atrophy. Common clinical manifestations of SWS include epileptic seizures, hemiparesis, visual field defects, glaucoma, developmental delay, and intellectual impairment. Sturge first described the clinical features of the disease in 1879,[1] whereas Weber demonstrated the pattern of intracranial calcification in 1929.[2] There is no known pattern of inheritance.

Cutaneous Features

The facial port-wine stain (PWS) is a congenital cutaneous lesion ipsilateral to the leptomeningeal angiomatosis (Figure 1). Classically, the facial PWS is found unilaterally involving one or more of the three divisions of the trigeminal nerve, but more extensive bilateral facial lesions, lesions involving the oral mucosa, or extracranial lesions involving the trunk and the extremities are also common. On the other hand, patients can have no facial PWS but have other typical clinical, neuroradiologic, and neuropathologic findings of SWS.[3,4,5] Although over 95% of patients with SWS have a facial PWS,[5,6] only 10% of patients with a facial PWS have an intracranial lesion.[7,8] Nonetheless, the diagnosis of SWS should be considered in every newborn with a facial PWS, although if the PWS spares the forehead and the upper and lower eyelids, there is a very low risk for subsequent development of neurologic and ocular complications.[8,9,10] Only one-fourth of patients with bilateral facial PWS have bilateral cerebral lesions.[11] However, the occurrence of a bilateral facial PWS is associated with an increased chance of hemispheral and bilateral cerebral involvement, and thus an increased likelihood of neurologic impairment as well as an earlier onset and a higher prevalence of seizures.[6,7] Bilateral facial PWS, especially when involving the upper and lower eyelids, is also associated with a higher prevalence of both unilateral and bilateral glaucoma.[6,7,11] The leptomeningeal angiomatosis and the facial PWS probably represent the abnormal persistence of an embryologic venous plexus,[12] since both the skin and the nervous system develop from the embryologic ectoderm.

Figure 1: *A child with bilateral facial port-wine stain involving all three divisions of the trigeminal nerve, more prominent on the right. Extracranial port-wine stain is also present on the trunk.*

Neurologic Manifestations

Epilepsy is the most important determinant of the management and prognosis of patients with SWS, and seizure control by anti-epileptic medications is often difficult.[5,13] It also plays an important role in the progressive mental and neurologic deterioration that is frequently present in children with SWS. Seizures are the most common neurologic manifestation, occurring in 75% to 90% of patients with SWS,[6,9,11,14,15,16] and it is the initial presenting symptom in 80% of patients.[5] Most children with SWS are neurologically normal for the first few months of life, but some patients can remain asymptomatic until adulthood. Sixty percent of children have the onset of seizure within the first year of life, and by the age of three, 80% of children will have experienced their first seizure episode.[6,12] However, a small number of patients can have the onset of seizures even in their second or third decade of life, and these patients usually have a more favourable mental prognosis.[6,12]

The first seizure is associated with a febrile episode in 30% of children, and fever can trigger subsequent seizures at any time during life.[11] The most common seizure type is partial motor seizures with or without Jacksonian march, with mainly clonic movements affecting the side of the body contralateral to the leptomeningeal angiomatosis.[13,17] Complex partial seizures, most commonly consisting of head rotation or eye deviation to the side opposite the angioma or initial motor phenomenon in extremities followed by loss of consciousness and often hypotonia, are frequently seen.[13] Secondary generalization of partial seizures to tonic-clonic seizures are also common. Myoclonic seizures, atonic seizures and infantile spasms occur less often,[11,13] and they are usually related to severe cerebral lesions and have a very early presentation.[11] Status epilepticus is not uncommonly seen as the presenting episode or one of the subsequent episodes.[13] Patients can have several types of attacks within a certain time period,[13] and the type of seizure may evolve during the course of the illness.[11,17]

The course of epilepsy is highly variable. Some patients continue to have frequent, regular seizures after the onset, while others can have clusters of seizures separated by prolonged periods of remission.[13,18] Children with hemispheral or bilateral cerebral involvement have a very early onset of seizures,[9,16] often within the first year of life. Seizures in these children are the most difficult to control and most of them are intractable to anti-epileptic drug therapy.[6] Children with seizures, especially beginning in the first year of life, usually have a poorer developmental prognosis and are also at higher risk of progressive mental retardation as well as significant psychosocial difficulties.[6,13] Mental retardation is present in 50% to 60% of patients with SWS.[13,16,19] As a general rule, children without seizures and those with late onset do not exhibit mental retardation[18] and are able to attain normal adult intelligence.[6] Presence of seizures and consequent intellectual limitations in patients seem to be an important factor in determining their ability to live independently.[6]

Hemiparesis is present in 40% of patients.[5,13] It often occurs shortly after the onset of seizures, and becomes progressively worse with continued recurrence of seizures and poor seizure control. The hemiparesis usually begins transiently, similar to postictal Todd paralysis, but it gradually requires longer periods to resolve and eventually becomes permanent.[12] It usually becomes more frequent with increasing age.[9,18] Arrested growth of the affected extremities or hemiatrophy often follows hemiparesis that occurs early in life.[12] Acute episodes of transient hemiplegia not associated with other features suggestive of epilepsy, but sometimes accompanied by headache, vomiting, or other migraine-like phenomena have also been reported.[13,20] The prevalence of migraine headache is higher in patients with SWS compared to the general population.[21]

Deterioration in neurologic status and cognition are believed to be related to the chronic ischemia-hypoxia of the brain resulting from circulatory abnormalities in the cortex underlying the leptomeningeal angiomatosis, and this is exacerbated by the increased metabolic demand during recurrent seizure episodes.

Ophthalmologic Complications

Glaucoma develops in up to 60% of patients with

Figure 2: *CT without contrast showing extensive cortical calcifications in the right hemisphere of the same child shown in figure 1.*

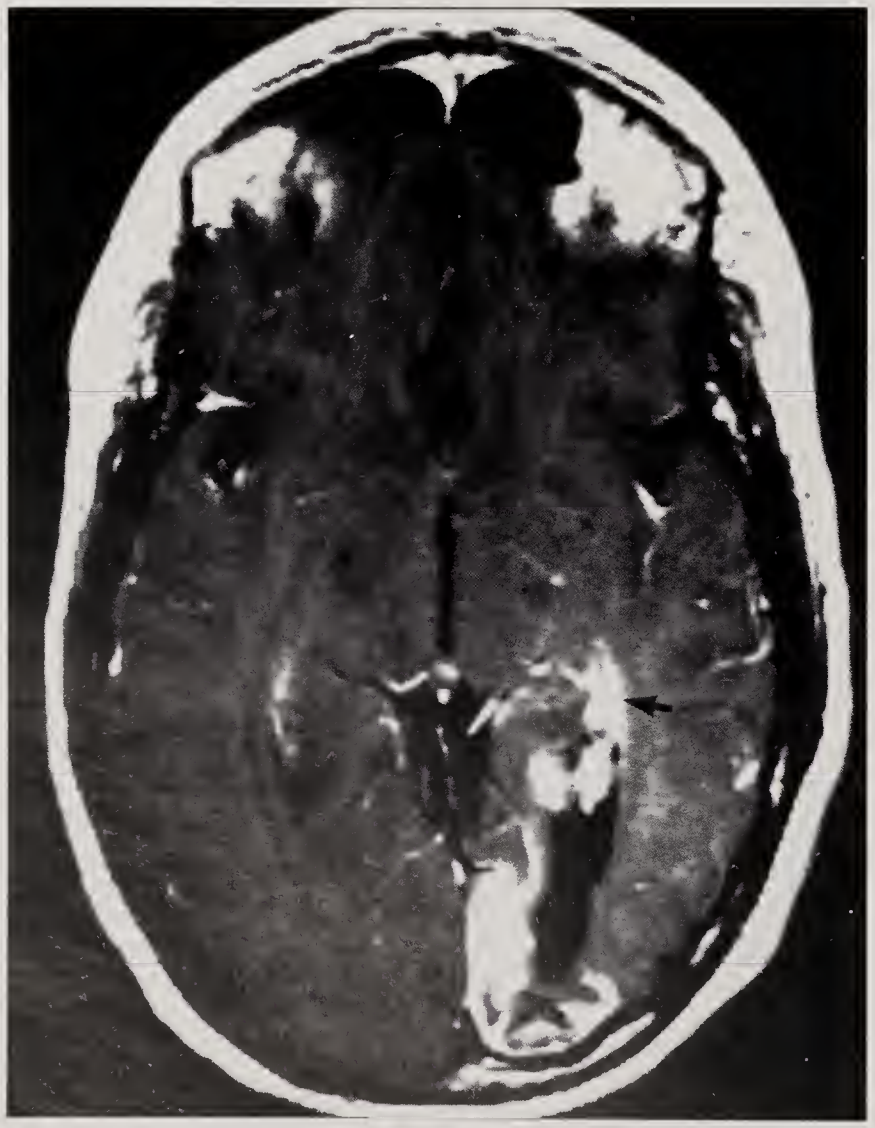

Figure 3: *MR with Gd-DTPA showing enhancement of the leptomeningeal angiomatosis in the left parieto-occiptal region (arrows).*

SWS,[6,22] and it is the initial presenting symptom in 7% of patients.[5] It may be present at birth,[12] and 40% of patients will have the onset of glaucoma within their first year of life, although 20% can have the onset of glaucoma after the age of 20.[6] Early onset glaucoma is often associated with abnormal anterior chamber angle, while abnormal development of the conjunctival and episcleral vascular tissues is often found in patients with late onset glaucoma.[23]

Homonymous hemianopsia occurrs in 60% of patients[13] and its onset often follows the initial manifestation of seizures.[12] It is the result of the frequent involvement of the occipital lobes by the leptomeningeal angiomatosis.

Conjunctival, episcleral, and choroidal hemangiomata are also common among patients with SWS.[23]

Diagnostic Evaluation

The clinical diagnosis of SWS is often straightforward if the patient has the characteristic facial PWS and the associated neurologic manifestations such as seizures. The minimum clinical and diagnostic criteria for SWS would require the presence of the intracranial leptomeningeal angiomatosis.[24] However, since a large proportion of children will have the PWS as an isolated finding and most children with leptomeningeal angiomatosis are initially normal,[12] neuroimaging studies and other tests are often useful for the diagnosis of SWS. In addition, neuroimaging studies can help in the planning of surgery by delineating precisely the extent of involvement by the leptomeningeal angioma and confirming that the cerebral involvement is unilateral.

The classical "tram-track" intracranial gyriform calcification is the radiographic hallmark of SWS (Figure 2),[12] and its presence and extent is better detected by CT than by MRI.[25,26,27] Cortical calcifications can be focal, most commonly affecting the occipital region.[12] Extensive and diffuse calcifications can also been seen throughout the affected hemisphere.[26] Increase in calcifications can be detected as the disease progresses.[26] Calcification is thought to occur secondary to hypoxia and ischemic injury,[28] possibly caused by the stasis of blood in the leptomeningeal angiomatous vessels.[29] Enhancement of the angioma can sometimes be seen on CT with contrast, but this is often obscured by heavy calcifications in the same region.[26]

With the advent of MRI with gadolinium contrast (Gd-DTPA), the direct visualization of the location and the extent of the pathognomonic leptomeningeal angiomatosis is possible (Figure 3). MRI with Gd-DTPA is becoming the method of choice in the diagnosis of SWS[25,26,30] and is also helpful in the selection of patients for surgical intervention.[31] The meningeal and cortical involvement are seen as areas of increased enhancement.[25,26] This area includes the leptomeningeal angiomatosis and the first cortical layer affected by gliosis.[25] The leptomeningeal angiomatosis most commonly involve the occipital and the temporal regions, and less often, the parietal and the frontal regions.[25,26] Hemispheric involvement by the angioma is

also common. Bilateral involvement occurs in 15% of children with SWS.[16] Increased signal in the white matter adjacent to the leptomeningeal angiomatosis can also be seen.[26] MRI with Gd-DTPA can detect affected zones of the brain and visualize small lesions in some patients before neurologic symptoms begin or neuroradiologic changes are observed on CT or MRI without contrast.[11,32] A normal study though, does not absolutely exclude the diagnosis of SWS.[12] In this situation, CT can be helpful to exclude the presence of cortical calcifications.[26]

Progressive cerebral hemiatrophy in the form of volume loss and/or prominence of sulci is commonly seen along the course of the illness. In older children with severe cerebral involvement, atrophy is associated with thickening and prominence of the cranial diploe on the affected hemisphere compared to the contralateral side.[25,26] Generally, cerebral atrophy can be detected equally well with CT and MRI, but if there is no coexisting prominence of sulci, CT may fail to detect the degree of volume loss.[25,26] Patchy parenchymal gliosis and demyelination accompanying the atrophy may also be seen on MRI.[28,33]

Parenchymal venous anomalies are also better seen on MRI than CT or conventional angiography.[25,26] A decrease or absence in the number of cortical veins[28,30] together with prominent deep medullary veins or subependymal veins can be visualized.[26,30] This is because the surface venous drainage of affected lobes is compromised by the leptomeningeal angiomatosis,[26] resulting in blood being shunted to the deep venous system via collateral vessels in a subependymal, periventricular or transparencyhmal location.[25] The development of this collateral drainage system may be a response by the brain attempting to preserve cortical function.[30] MRI is also superior to CT in demonstrating presumed ischemic changes affecting the gray and white matter.[26] A recent study has advocated the use of MR angiography because of its ability to demonstrate the venous anomalies in greater detail and to facilitate an earlier diagnosis before any neurologic manifestations.[34] Progressive venous occlusion has also been demonstrated using MR venography.[35] The use of these new angiographic techniques and the resulting findings have to be substantiated by further studies regarding its benefits over the conventional neuroimaging modalities and the significance of the additional information obtained.

Enlargement and increased enhancement of the choroid plexus is another common finding on neuroimaging studies in SWS.[36] It can be demonstrated efficiently by both CT and MRI with contrast administration.[25,26] Cyst formation is occasionally seen within the choroid plexus.[26,37] Larger choroid plexus size has recently been found to be associated with increased cortical involvement by leptomeningeal angiomatosis and increased extent of atrophy.[37] Diffuse choroidal hemangioma can also be detected by MRI as abnormal ocular enhancement, and they may also be seen on fundoscopy.[38] In early SWS, accelerated myelination can be detected by MRI in the areas underlying the leptomeningeal angioma.[39] It has been suggested that this MRI pattern can be helpful for the early diagnosis of SWS.[39]

MRI is found to be more efficient in the detection of findings related to the clinical status of patients: seizure control, degree of psychomotor development, and the degree of hemiparesis.[25] Poorer clinical status is associated with increase in white matter alterations, increase in the extent of lobar involvement by leptomeningeal angiomatosis, and increase in the degree of parenchymal atrophy.[25]

EEG is helpful in confirming cerebral involvement and localizing the lesion.[12] Over 95% of patients with SWS have abnormalities seen on EEG.[13] The most common EEG finding is the asymmetry of background activity, with attenuation and slowing over the whole cerebral hemisphere or part of the hemisphere.[9,11] This asymmetry can be observed from the first months of life, but is more noticeable as cerebral hemiatrophy becomes more severe.[11] The occipital and temporal regions are most often involved.[13] Focal paroxysmal epileptiform spikes mainly occur in the hemisphere affected by the leptomeningeal angioma, but the spikes can be bilateral in patients with clinical and neuroradiographic evidence of unilateral disease, or even confined to the contralateral side in some cases.[11,13] Some children may have bilateral synchronous spike-wave or polyspike-wave activity without any consistent localizing features.[18]

Interictal SPECT or PET generally shows a significant decrease in cerebral perfusion or glucose metabolism in the affected brain areas,[40,41,42,43] although transient hyperperfusion on SPECT has been reported.[39,44] SPECT may sometimes reveal a larger affected area than MRI with Gd-DTPA.[40] These functional neuroimaging techniques can be helpful in the evaluation of patients preceding surgery.[12]

Neuropathology

On gross examination, the leptomeninges are thickened and hypervascularized.[12] Microscopically, the angiomatosis consists of a proliferation of ectatic thin-walled vessels,[45] with a capillary or venous morphology (Figure 4). These abnormal vessels are sometimes occluded by hyalinization or subendothelial proliferation.[46] Similar prominent vessels can also be found in an intraparenchymal location and in the choroid plexus.[47]

Calcifications are typically seen in the neocortex underlying the leptomeningeal angiomatosis (Figure 5),[47] but it can also be found sometimes in subcortical white matter.[46] They are often located in a pericapillary distribution.[47] They can be found within the wall of the abnormal vessels and within the neuropil. Calcifications are usually accompanied by neuronal loss and astrogliosis (Figure 5).[45] Cortical thinning and gyral atrophy in the affected regions are also common.[47]

Figure 4: Leptomeningeal angioma with thin-walled venous channels. *(H&E 112x)*

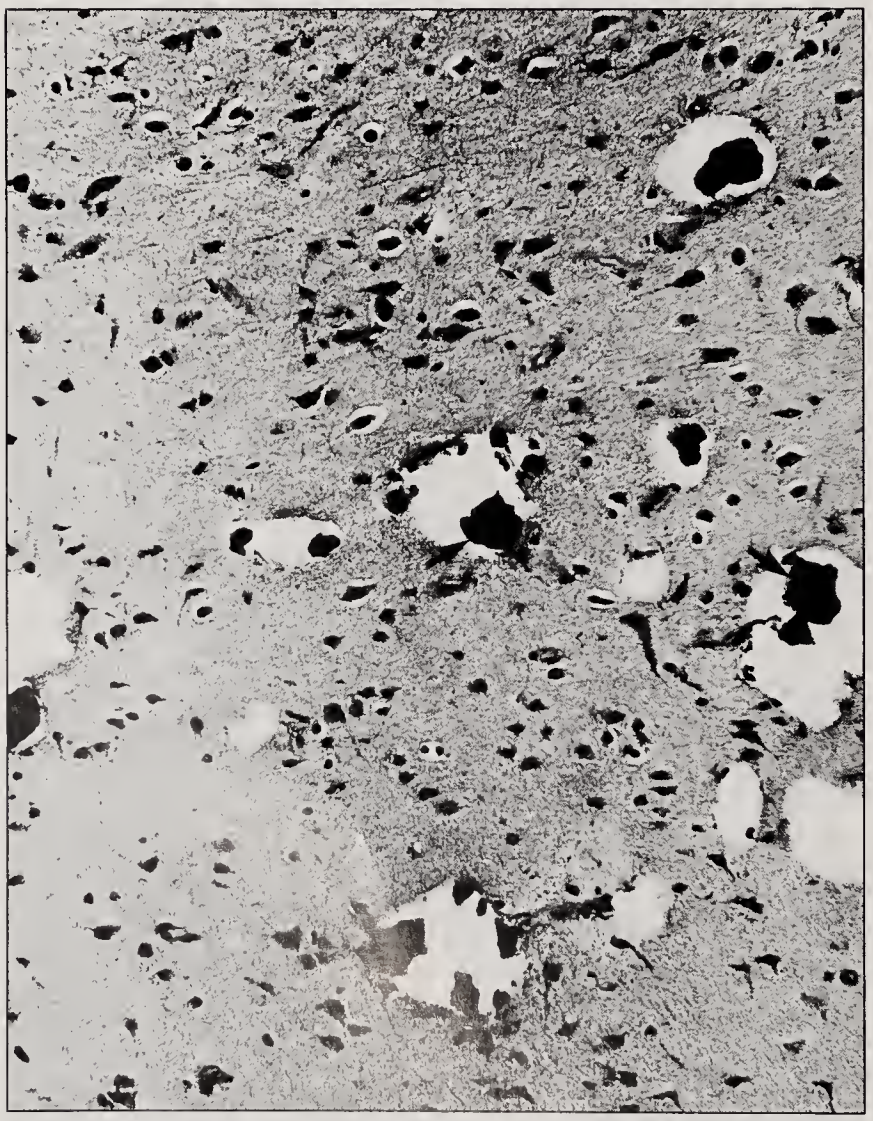

Figure 5: Neuronal dropout and gliosis with cortical calcifications (arrows). *(H&E 225x)*

Management

Anti-epileptic medication is the initial treatment irrespective of the age of the patient, although complete control of seizures is only achievable in 10% of patients.[5] Less than 1% of non-surgical patients can have drug treatment discontinued successfully without recurrence of seizures.[13] The choice of anti-epileptic drug is dictated by the specific seizure type. Carbamezapine is the drug of choice for the initial treatment if the seizures are focal in origin, because of its more favourable side effect profile over phenytoin. For generalized seizures, valproic acid is often helpful, although children under two years of age who are on polytherapy and who have a neurologic handicap have increased risk of developing fatal hepatotoxicity.[48] Surgery provides good seizure control when drug therapy fails. Timing of surgery is crucial because epilepsy is the most important factor leading to the clinical deterioration and the subsequent handicap seen in children with SWS.

Patients with SWS who have seizures intractable to anticonvulsant medication or those who have a progressively deteriorating clinical course with worsening of motor function should be considered for surgical resection of the affected cortical regions. For infants less than one year of age with intractable seizures, surgery should not be delayed for more than a few months.[13]

In patients with extensive involvement of the whole hemisphere demonstrated by appropriate neuroimaging studies, hemispherectomy (hemidecortication) is the procedure of choice. Hemispherectomy performed during the first year of life can prevent an otherwise unremitting clinical deterioration.[49] Eligibility for hemispherectomy is based on four criteria.[50] First, the seizures must be intractable to anticonvulsant therapy. Second, the patient should exhibit clear evidence of hemiplegia contralateral to the hemisphere from which the seizures are arising. Third, the patient should exhibit evidence of neurodevelopmental retardation consistent with delay or arrest of maturation owing to interference by frequent seizures. Finally, structural and functional tests must demonstrate diffuse abnormality of the cerebral hemisphere contralateral to the patient's hemiparesis, with the ipsilateral hemisphere being shown to be structurally and functionally normal. Video EEG telemetry, median nerve sensory evoked potentials, and visual evoked potentials are helpful in this regard in addition to functional neuroimaging techniques such as SPECT or PET. The Wada test can also be helpful to confirm that language is lateralized to the hemisphere ipsilateral to the hemiplegia and to determine whether the intact hemisphere is capable of supporting memory after resection of the opposite side.[50] If the patient has independent epileptiform discharge in the intact hemisphere, amobarbital suppression may be used to test whether these will disappear after suppression of the abnormal hemisphere.[50]

Over 80% of patients are seizure-free or only have occasional seizures after hemispherectomy.[9,17,49,51] Anticonvulsant medications can usually be discontinued successfully shortly after surgery in patients who are seizure-

free, although some may need continued medical treatment for complete seizure control.[17,51] Motor function often improves or remains unchanged in most patients after hemispherectomy.[9,51] Many patients regain the ability to ambulate and to use the proximal portion of the upper limb or are able to acquire these abilities if they were too young to have developed them before surgery.[50] However, hand function with digital dexterity does not return.[50] Occasionally, patients can have worsening of motor function after hemispherectomy, but this is not significantly worse compared to medically-treated patients.[9] In addition, the incidence of normal or borderline intelligence is much higher in surgically treated patients than patients remaining on anticonvulsant therapy, especially when surgery is performed at an early age.[9,17] Evidence of developmental brain plasticity in terms of reorganization of descending motor pathways[52] and metabolic recovery in the caudate nucleus ipsilateral to the resected hemisphere[53] has recently been demonstrated in humans, which give further support for early hemispherectomy as soon as seizures become intractable. Further studies are needed to determine the critical period for surgery in which brain plasticity is optimal for the recovery of function.

If the cerebral lesions are localized, focal cortical resection is usually employed. It is crucial to resect the entire brain area affected by the leptomeningeal angioma and the associated epileptogenic brain tissue, as incomplete resections can result in recurrence of seizures after surgery.[13] Intraoperative electrocorticography (ECoG) can be helpful in this regard. As with hemispherectomy, patients often have excellent seizure control after focal resection.[13]

A small number of patients may have post-operative complications such as hydrocephalus or subdural effusion after hemispherectomy, which may require permanent shunt placement.[9,17] Hemianopsia can result from resections involving the occipital lobe, although most children already have visual field defects prior to surgery due to occipital involvement by the leptomeningeal angioma.[13]

Medical control of glaucoma is difficult, and most patients require operative intervention. Repeated examinations under sedation or general anaesthesia are necessary until an age is reached where office examination is feasible.[23] Goniotomy or trabeculotomy does not yield results comparable to those achieved in primary congenital glaucoma.[54] Results of trabeculectomy have been inconsistent.[54] Combined trabeculotomy-trabeculectomy gives excellent results as it removes the possible obstruction to the aqueous outflow due to a congenital angle deformity (trabeculotomy) and also bypasses the episcleral venous system (trabeculectomy).[54] Use of medication postoperatively may be needed to achieve complete control of intraocular pressure.[55] It is important to have periodic ophthalmologic evaluations to monitor any increase in intraocular pressure since the onset of glaucoma can be late.[6] When performing routine examination or surgical procedures for glaucoma, anaesthesia should be planned to avoid trauma to the hemangiomata during intubation, because uncontrolled hemorrhage may result from the rupture or perforation of angiomata in the oropharynx.[56] Anaesthetic agents which may increase the intraocular pressure should be avoided.[56] Careful intubation and extubation is essential to prevent any increase in intraocular as well as intracranial pressure.[56]

The facial PWS may represent a tremendous cosmetic problem, particularly in adolescent patients with well-controlled seizures and normal intelligence.[57] Significant psychopathology can be present, complicating quality of life.[58] Laser therapy is the preferred treatment to minimize the facial PWS. Ideal candidates are those children with reasonably good neurologic function who have a small lesion.[12] Opaque cosmetics may help to mask a flat PWS in patients who cannot undergo laser therapy.[57]

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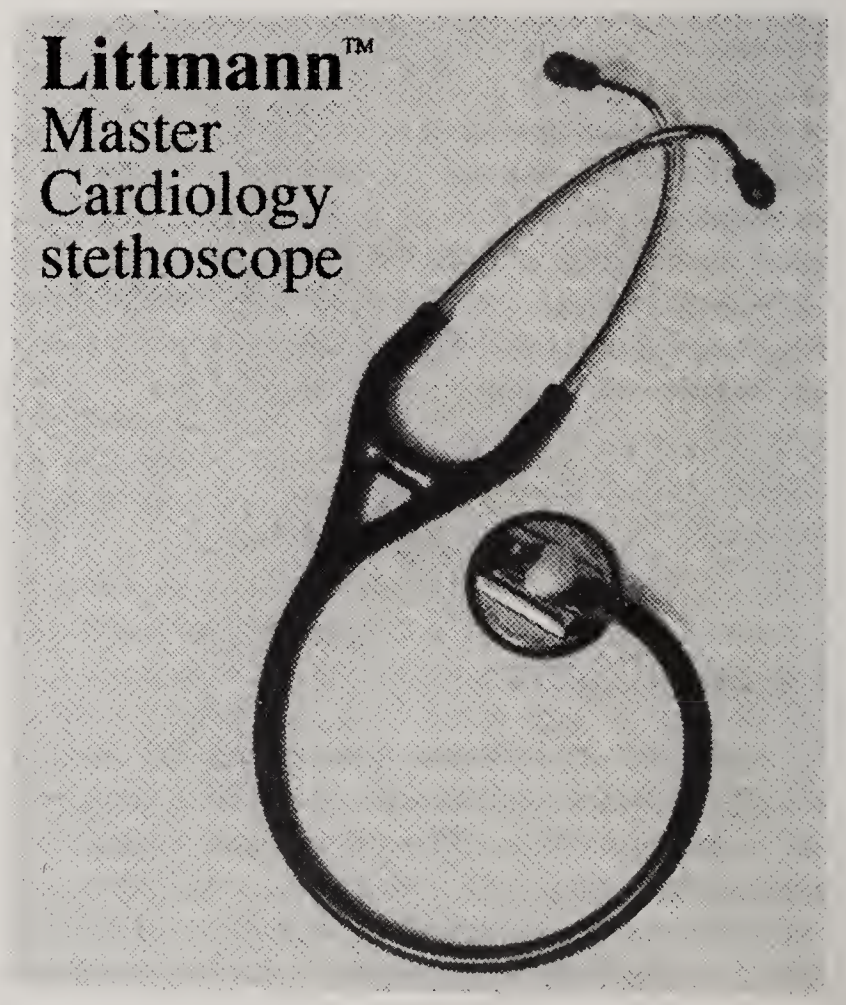

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A Consensus Protocol for the Diagnosis of Pulmonary Embolism

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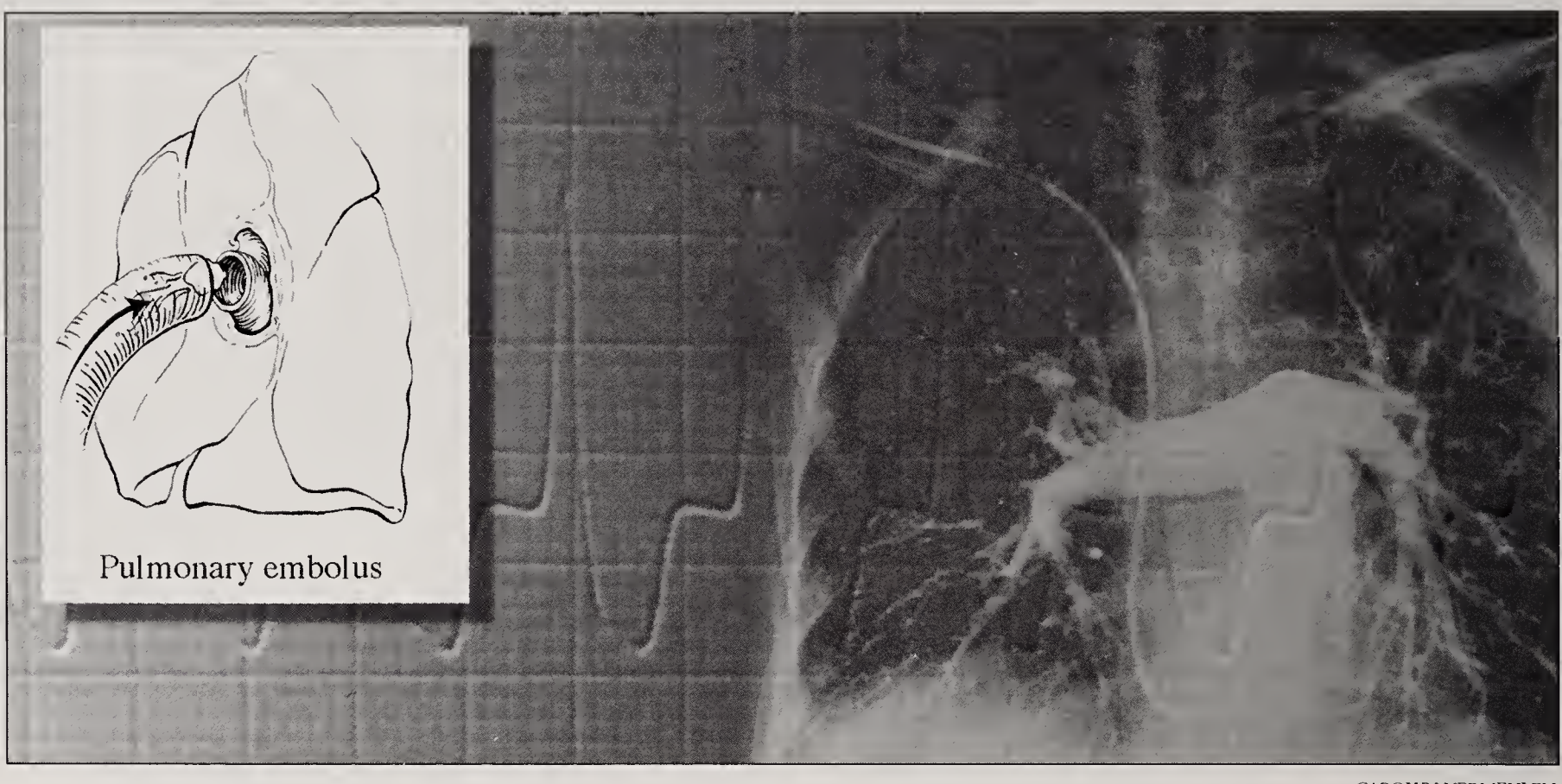

CAROLYN VERMEULEN

Abstract

Pulmonary embolism (PE) is a serious medical condition that causes approximately 30,000 deaths annually in the United States alone.[1] Due to its nonspecific clinical manifestations, the diagnosis may be difficult; close to 20% of patients will die because it is missed.[1] The ability to reach a prompt diagnosis is also hampered by the lack of an accepted investigation algorithm. This article outlines the current methods used in diagnosing PE with a review of laboratory and imaging tests, citing their efficacy. The evidence obtained from recent trials, review articles, and meta-analyses, is synthesized to construct a suggested approach to the accurate and efficient diagnosis of acute pulmonary embolism.

Background

Pulmonary embolism (PE) is the sudden lodgement of embolic material in a pulmonary artery with subsequent obstruction of blood supply from that vessel. The most common type of pulmonary embolus is a dislodged fragment of thrombus usually formed in a leg or pelvic vein. A variety of other substances are responsible for a small percentage of cases of emboli including talc granules and cotton fibres injected along with illicit drugs, blood-borne parasites like schistosomes as well as septic and amniotic fluid emboli.

The clinical manifestations of PE are nonspecific and vary in frequency and intensity - they depend largely on the extent of pulmonary vascular occlusion as well as preembolic cardiopulmonary function. Small thromboemboli may be asymptomatic; for this reason the diagnosis of PE is often missed in sick hospitalized patients. The clinical diagnosis of deep venous thrombosis is also highly inaccurate, as physical examination is often misleading.[1] Clinical evaluation is further impeded by incomplete information concerning the incidence of PE in many populations.[1,3,4] The presence of predisposing or comorbid conditions is often less helpful than is generally believed to the clinician

who is considering the diagnosis of PE in a particular patient.[5] The importance of establishing a prompt accurate diagnosis and instituting therapy only truly comes into perspective when it is estimated directly or indirectly; PE causes 200,000 deaths per year.[1] Many of these deaths are a consequence of complications following missed cases of PE.

Diagnosis

Due to the lack of clinical sensitivity and specificity, the diagnosis of PE is difficult to establish without using special procedures. The differential diagnosis in patients with massive PE includes cardiac tamponade, acute myocardial infarction, and septic shock. When infarction of lung parenchyma occurs secondary to the PE, the differential diagnosis must include pneumonia, atelectasis, congestive heart failure, and pericarditis. A systematic clinical approach, however, is important to reach a prompt and accurate diagnosis as the complication of thrombosis is sudden, unexpected death. Often this result could be prevented by anticoagulation therapy had the presence of the condition been known. However, the anticoagulants used for therapy of PE are associated with potentially dangerous side effects and so should be given only when there is strong suspicion of PE.[6]

Tests

A) Symptoms and Signs

Dyspnea and chest pain are the only symptoms reported by more than 50% of patients with pulmonary embolism.[7-10] Tachypnea, tachycardia, and focal changes in breath sounds – rales are the most commonly observed signs and are equally nonspecific.[7-10] Other signs and symptoms include hemoptysis, pleuritic chest pain, syncope, and cardiac arrhythmias, but occur less frequently and also are not unique to pulmonary embolism. It is important for the clinician to consider the presence of conditions predisposing to deep vein thrombosis (DVT) such as congestive heart failure, malignancy, recent orthopaedic surgery resulting in immobilty, and family history. With all of the above taken into account, the diagnosis of PE cannot be made from history and physical alone;[5] further investigations are necessitated. These are cited below.

B) Chest X-ray

An antero-posterior (AP) and lateral chest x-ray is the first imaging study performed in the workup of PE. Greenspan et al. showed that the sensitivity of the chest x-ray was 52% with a range of 33-88% and the specificity was 59% with a range of 31-80% in the diagnosis of PE.[11] Hence, clinical experience and multiobserver evaluation[11] have demonstrated that the chest radiograph is not reliable for diagnosis of PE. However, the chest film remains necessary to rule out conditions that may clinically mimic pulmonary embolism such as pneumonia or pneumothorax,[12] and is essential for the proper interpretation of the ventilation/perfusion (V/Q) scan.

C) Laboratory Investigations

The subsequent investigation is an arterial blood gas (ABG) determination. The alveolar-arterial oxygen gradient (A-a gradient) established from ABG determinations can help in directing further tests. As a single test, it also is unreliable to establish a diagnosis as it is unable to discriminate patients with PE from those with other disorders.[12-14] Elevated LDH may be demonstrated in as many as 85% of patients with PE and pulmonary infarction, but is nonspecific to this condition as it also occurs in heart failure, shock, pregnancy, renal and liver disease, anemia, pneumonia, and carcinoma.[14] D-Dimer levels or fibrin split products have been proposed as a diagnostic test for PE, analogous to serial creatine kinase measurements in the diagnosis of myocardial infarction.[15] The current literature, however, shows D-Dimer levels to be a very sensitive, but nonspecific test.[15] Goldhaber et al. showed that the D-Dimer was only useful in screening patients with suspected PE who required pulmonary angiography. Thus, despite its sensitivity, D-Dimer levels are not standard in the workup of suspected PE.

D) Electrocardiogram

An EKG is then performed to exclude myocardial infarction and pericarditis. It may often show right ventricular strain, but nonspecific ST and T wave changes are more common.[2] The EKG in massive acute PE may show right axis shift with ST changes in lead I, Q waves and T wave abnormalities in lead III (S1Q3T3 pattern), or incomplete right bundle branch block, but it does not show right ventricular hypertrophy (RVH) - RVH by EKG takes months or years to develop. The EKG may also demonstrate a tachycardia that is often found in PE, but the clinician must be cautioned that in many instances, the EKG can be entirely normal. In summary, the EKG as a diagnostic tool, can show patterns indicating PE, but is not diagnostic of the condition.

E)V/Q Scintigraphy

The suspicion of PE by clinical and chest radiographic evaluation in a patient by this point in the workup can be highly likely, possible, or unlikely. However, as discussed, these criteria alone cannot reliably make or exclude the diagnosis. The V/Q scan, which reflects the characteristic physiologic derangement in PE – nonperfusion of ventilated lung segments – is more accurate than any other noninvasive method.[14] The perfusion lung study provides a visual representation of the relative distribution of pulmonary arterial blood flow. The Prospective Investigation of Pulmonary

Embolism Diagnosis (PIOPED) study, a multicenter, prospective effort concluded that with all categories of "% probability of PE as assessed by clinical exam" combined, a high probability V/Q scan demonstrates evidence of PE in 87% of cases, the intermediate probability V/Q scan in 30% of cases, the low probability V/Q scan in 14% of cases and the near normal/normal scan in 4% cases.[17] In summary - the high-probability scan usually indicates pulmonary embolism; the low probability scan with a strong negative clinical impression makes the possibility of PE less likely; indeterminate scans are of no help in establishing a diagnosis. In cases of indeterminate scans, a pulmonary angiogram is required. Thus, much of the value of the V/Q scan lies in the finding that a normal perfusion scan excludes PE.[18]

F) Pulmonary Angiography

As mentioned previously in cases of indeterminate scans, often a pulmonary angiogram is required. Pulmonary angiography remains the most specific and sensitive diagnostic procedure available for pulmonary embolism when performed early in the course of disease.[19] If there has been a delay in the angiographic procedure, partial or complete lysis of the embolus may have occurred before the study is performed and the sensitivity and specificity of the test is decreased.[19]

The single diagnostic criteria of PE on pulmonary angiogram is intra-arterial filling defect secondary to complete obstruction of pulmonary arterial branches. Other frequent findings include partial obstructions and increased proximal calibre/decreased distal calibre, but these findings are noninterpretive.[19] When read by a panel of experts and subjected to reevaluation in cases of disagreement, pulmonary angiograms were falsely negative in only 1 to 2 percent of patients.[20,21] In summary, the goal of pulmonary angiography is to provide a definitive diagnosis on which management decisions concerning PE can be based. When conducted promptly, the pulmonary angiogram is considered to be the diagnostic 'gold standard'.

Consensus Protocol

In an attempt to aid the clinician, from medical student to staff, in diagnosing PE, we have developed a consensus protocol with the Department of Medical Imaging and Division of Respirology at Mount Sinai Hospital. This protocol reflects the current literature and allows a systematic workup of a patient with suspected pulmonary embolism. It eliminates the use of unnecessary laboratory and imaging studies. In addition, it provides the appropriate indications for consultation of appropriate specialists and prevents time delays that can be critical in the course of the patient's disease.

Table 1

Consensus Protocol for Evaluating Patients With Suspected Pulmonary Embolus

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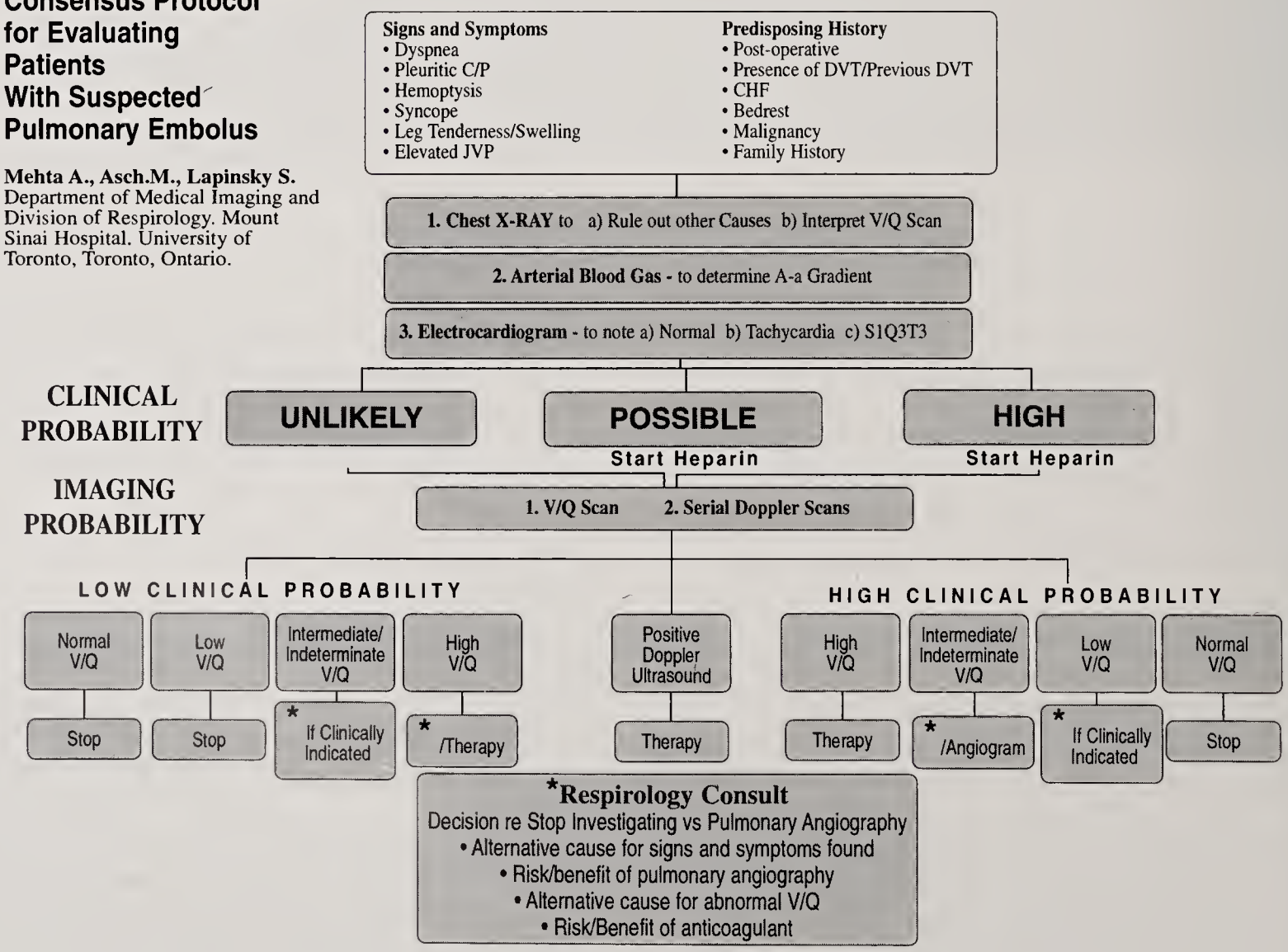

Prognosis

Available data suggest that approximately 600,000 individuals each year in the United States have a pulmonary thromboembolic event.[22] An estimated 450,000 survive.[22] Of these, only 35% are estimated to have had the diagnosis made and treatment instituted.[1] Mortality following an initial embolic event varies with the extent of embolization and the patient's preexisting cardiorespiratory status. The likelihood that a patient compromised with cardiorespiratory function will die following significant embolic events is high, on the order of 25%, if not treated expediently.[23] If a patient has normal cardiorespiratory status, he/she is unlikely to die unless the occlusion exceeds 50% of the pulmonary vascular bed.[24] When the initial embolic event is fatal, death occurs within 1 to 2 hours. Patients in whom the diagnosis is not made can later suffer complications of PE including chronic cor pulmonale (pulmonary hypertension, right ventricular failure without left ventricular failure) and pulmonary infarction.[11] It is hoped that with the advent of this consensus protocol, diagnosis will become more accurate and efficient and assist in preventing missed diagnoses and subsequent complications.

Discussion and Conclusion

The optimal approach to the diagnosis of pulmonary embolism remains controversial. It is well documented that the clinical symptoms and signs and results of routine laboratory studies are of limited value for diagnosis because of their nonspecificity and/or insensitivity. The findings on chest radiography are also quite nonspecific. With the publication of the PIOPED study, the utility of the V/Q scan has been determined. The pulmonary angiogram is generally acknowledged be the definitive means of diagnosis, however, it is performed in relatively few patients due to its invasive nature and expense. Lastly, due to the lack of consensus approach, in most hospitals the frequency of suspected pulmonary embolism far exceeds the capacity to perform pulmonary angiography. Yet, with the analysis of all the modalities of investigation for PE, numerous autopsy studies still indicate that PE is considerably underdiagnosed.[25] There is evidence to indicate that the immediate and subsequent intended institution of anticoagulation in patients with acute PE significantly reduces the associated morbidity and mortality;[26,27] however over the past decade, the fatality rates of PE have not been reduced.[28] The utility of this standard protocol becomes clearly evident.

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The Role of Ambulatory Blood Pressure Monitoring in Clinical Practice: An Evidence Based Approach

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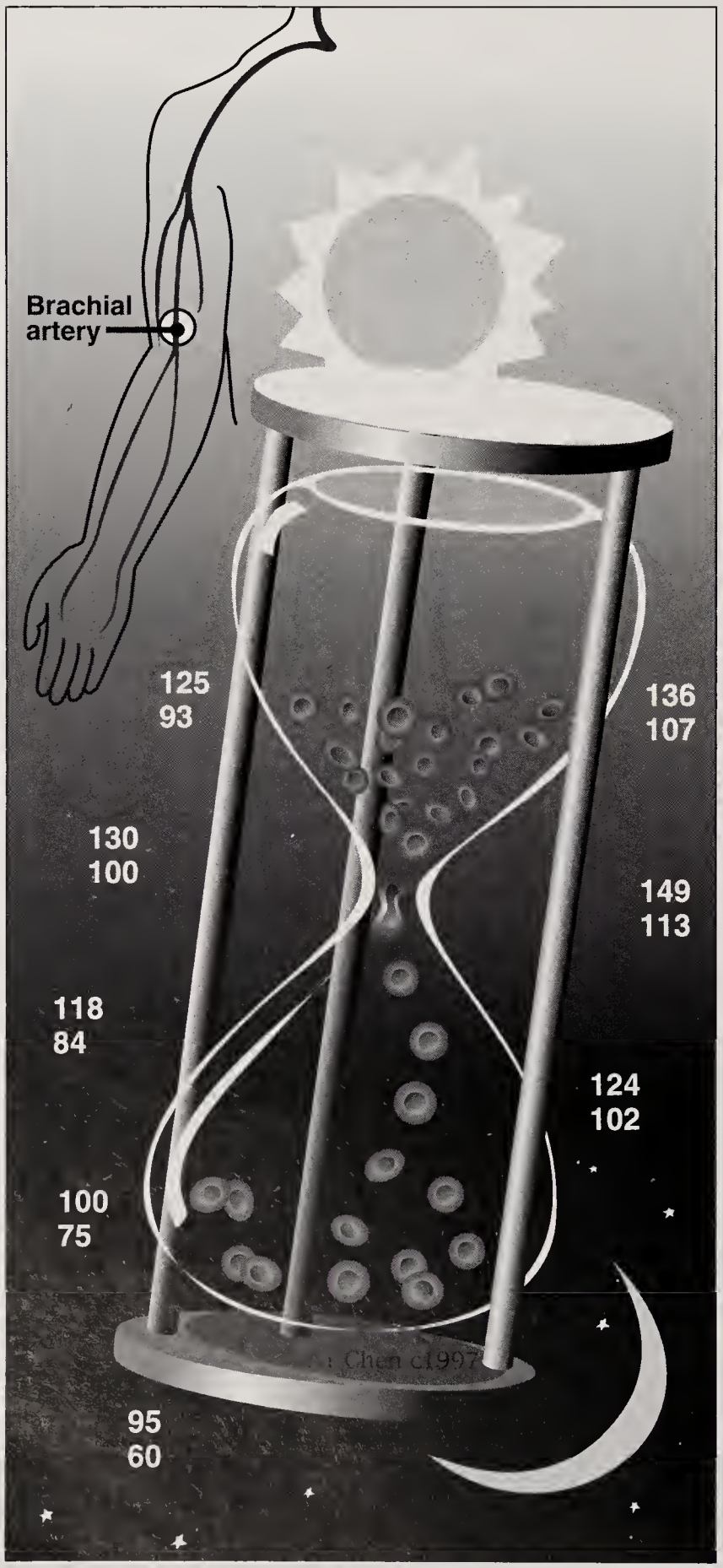

ALICE CHEN

Abstract

Ambulatory blood pressure monitoring (ABPM) is gaining increasing popularity in the management of patients with suspected hypertension. It allows for the non-invasive measurement of blood pressure patterns over a 24 hour period with high validity and reliability. The validity of commonly available ABPM products has been established in accordance with international standards. ABPM reliability exceeds that of clinic measurements, as ABPM is subject to fewer influences that reduce intrapatient reproducibility of blood pressure readings. Clinically, this technology may be of use in selected aspects of hypertension management, including the evaluation of mildly hypertensive patients without target organ damage and the assessment of patients resistant to hypertensive therapy. Studies, currently ongoing, will help to define normal ABPM values and the prognostic significance of new blood pressure parameters measured by 24 hour monitoring including variability, load, and diurnal fluctuations. Thus, although ABPM has important uses in the care of hypertensive patients, its role will continue to evolve as further research data on its efficacy become available.

Introduction

Hypertension is an extremely common medical condition. Since blood pressure (BP) is highly variable, the accurate diagnosis of hypertension is often a challenge.[1] This is compounded by an alarm reaction often experienced by patients when measurements are taken by a physician in a clinic - the so-called "white coat" effect.[2] Ambulatory blood pressure monitoring (ABPM), a technique that measures blood pressure over a 24 hour period, has become more widely used in patient care.[3] As this technology may have many uses and potential misuses, it is important to define its specific role in clinical practice.

The case examples are of patients seen at an ambulatory clinic at The Toronto Hospital - Western Division. They are typical of hypertensive patients in whom clinicans may consider ordering ABPM. Case 1 is a 53 year old male with

newly diagnosed hypertension, a mean of three clinic blood pressures (BPs) of 145/90 and left ventricular hypertrophy (LVH) on his EKG. Case 2 is a 72 year old female with mean of three clinic BPs of 168/86 who is otherwise healthy. Case 3 is a 56 year old female on high dose acebutolol and enalapril with persistently high clinic BP readings of 158/94. This paper will help determine which of these patients would have benefitted from ABPM.

This paper, following an evidence based approach to determining the utility of a new diagnostic test, will consider if: (1) the test method has been adequately described, (2) validity and reliability of the test have been determined, (3) a normal blood pressure value has been defined, (4) the utility of the test has been proven in making accurate diagnoses, providing prognostic information, and/or supporting the selection of efficacious treatment.[4]

Description of Technology

ABPM devices are lightweight, portable devices that can record BP over a 24 hour period (Figure 1). Currently available equipment records blood pressure intermittently, inflating at a programmable frequency of four to eight times per hour while awake and two to four times per hour during sleep. Ausculatory methods that use one or more microphones to detect Korotkoff sounds, and oscillometric methods, that detect initial and maximal brachial artery vibrations, are employed.[5]

Data stored in the device can be downloaded into a computer and the results printed. The results generated include the mean and standard deviation of 24 hour systolic blood pressure (SBP) and diastolic blood pressure (DBP), day and nighttime blood pressure means, the percentage of systolic readings greater than 140 mmHg and of diastolic readings greater than 90 mm Hg.[6]

Validity

Validation protocols have been established by the American Association for the Advancement of Medical Instrumentation (AAMI) and the British Hypertension Society (BHS). These validation standards involve multiple comparisons with mercury manometer blood pressure measured in many patients in different positions by different observers.[7] Of the 43 devices currently on the market, 18 have been validated according to one of these protocols and 9 according to both.[8]

Reliablity

Reliablity depends on the degree to which test results can be performed reproducibly in individual patients. The reproducibility of clinic BP is low for several reasons: they are subject to marked variability in blood pressure due to posture, time of day, environment, emotional state, and ingestion of food and drugs; the white coat effect in the clinical setting; and digit preference, where BP readings ending in 0 or 5 are preferentially recorded.[5] ABP is based on a greater number of measurements and includes a wide range of activities and thus has a greater within-subject reproducibility than clinic readings. Studies of short term reproducibility have consistently shown greater reproducibility of ABP.[9] A recent long term reproducibility study has shown that the correlation coefficient of systolic BP (SBP) and diastolic BP (DBP) over a two year period was 0.87 and 0.90 for ABP compared to 0.48 and 0.31 for clinic blood pressures.[10]

Definition of Normal

Hypertension, defined as that level of blood pressure below which treatment does more harm than good, is 140/90 mmHg for people under age 60.[11] This finding is based on prospective epidemiological studies and clinical trials that have employed clinic blood pressure measurements. Data to define ABP norms in an analogous manner are not yet available. In the absence of such prospective studies, alternative definitions have been proposed. One is a percentile definition, where an abnormal ABP is defined as the 90 or 95th percentile of the population distribution. A meta-analysis of 23 studies involving 3476 normotensive individuals gave an upper limit of normal of 139/87 mmHg for 24 hr ABP and 146/91 mmHg for daytime ABP.[12] In a percentile approach to defining normal, the arbitrary cutoffs set are not related to risk of clinical outcomes. In addition, the prevalence of hypertension is set at 5%, when in fact, the prevalence in Canadians, defined by clinic measurements, is closer to 15%.[13]

Cardiovascular risk has been related only to clinic pressures because this measurement system is used in all epidemiological studies relating blood pressure to morbidity. Thus

Figure 1: *An example of an ABPM device.*

an alternative approach is to define the cut off for an abnormal ABPM as the level equivalent to a clinic pressure of 140/90 mm Hg. Correlation studies have been done that relate the two measurements and suggest that a daytime mean ABP of 135/85 mm Hg is an appropriate cutoff.[14]

Test Utility and Indications

A diagnostic test may contribute to accurate diagnosis, provide information about prognosis, and support the application of specific efficacious treatments, thus leading to better clinical outcome for the patient. No data exist yet on the impact of ABP on clinical outcome. Canadian recommendations published in 1993 were very cautious stating that "further, higher quality research should be undertaken to determine if ABPM should replace or supplement traditional techniques for the diagnosis of mild hypertension".[11] More recently, leading authorities and societies[1,6,15] have taken a more positive view of ABPM in light of newly published evidence and accumulating experience. The American College of Cardiology has endorsed ABPM as a "mature, clinically useful technique for the management of selected hypertensive patients".[15] Commonly agreed upon indications for ABPM are covered below and emerging controversial areas are highlighted.

Diagnosis

ABPM has a role to play in the evaluation of patients with borderline hypertension. These patients generally have mild to moderate hypertension without target organ damage and the decision to treat them hinges on the actual blood pressure readings obtained. ABPM may be helpful in these patients to separate those with true sustained hypertension from those whose pressures are disproportionately elevated in clinic readings.[16] This latter group of patients has been referred to as white coat hypertensives.

White coat hypertensives have elevated office blood pressure measurements and normal ambulatory pressure, defined more stringently as three weekly sitting office DBP of greater than 90 mmHg and average ABPM pressures less than 85 mmHg and 15 mmHg less than averaged office measurements.[16] White coat hypertension is believed to reflect an exaggerated pressor response to stressful stimuli. The prevalence is estimated to be 20 to 40% in patients who present with mild to moderate hypertension. It tends to be more common in women[17] and among the elderly.[18] Although patients with white coat hypertension are not presently treated with antihypertensive medications, it remains controversial if white coat hypertension is a truly benign condition. Further research is needed to clarify this issue.

There are several other clinical scenarios in which ABPM may prove of value. It can be used to investigate patients with intermittent symptoms related to blood pressure. This may be when transient hypotension is suspected in patients on antihypertensive medications or when episodic symptoms of hypertension occur due to panic attacks or a variety of other causes.[15] A diary log book that correlates symptom onset with blood pressure measurement can be helpful. Published studies have investigated the role of ABPM in monitoring blood pressure change in pregnancy[19] and evaluating certain secondary causes of hypertension.[20]

Prognosis

Multiple cross-sectional studies have shown a higher correlation of ABPM than clinic blood pressures with hypertensive target organ damage, including the heart, kidneys, brain, and blood vessels.[21] Due to their design, these studies are limited to showing associations. However, prospective studies on these questions are underway. These include the Office vs Ambulatory trial, a substudy of the Syst-Eur trial of isolated systolic hypertension, and the HARVEST study. These studies will provide further data on the predictive value of ambulatory monitoring for cardiovascular events.[6]

Treatment

Patients who are resistant to hypertensive treatment, having persistently elevated clinic pressures despite the use of multiple medications to control blood pressure, represent a challenging management problem. ABPM is appropriately used in the evaluation of such patients, helping to differentiate genuinely resistant hypertension from those with an exaggerated white coat effect.[1]

Potentially important and valuable applications are being developed to use 24 hour blood pressure data to target dosing and drug selection to individual patients needs. ABPM may be of use in evaluating the extent of 24 hour control of blood pressure and may aid in the selection of certain medications more suited to this purpose.[22]

Additional Parameters

ABPM reports provide a plethora of data not previously available that may be of importance in diagnosis and treatment of hypertension. These include measures of blood pressure variability (standard deviation or coefficient of variance), blood pressure load (the percentage of readings that are greater than 140/90 mm Hg while awake and greater than 120/80 mmHg while asleep), and patterns of diurnal variations in mean blood pressures.

The importance of blood pressure variability as a risk factor for cardiovascular mortality is being investigated. One study has shown that blood pressure variability is correlated with organ damage and predictive of progression in prospective follow-up.[23] These data are still preliminary and the effects of modifying variability with antihypertensive medications remains unexplored.[18] Increased blood pressure loads pre-

dict target organ damage in mild to moderate hypertensive patients. However, this measure has low reproducibility and its importance is also still uncertain.[6]

ABP can document the extent of diurnal variation in blood pressure. Normally, blood pressure values fall during the night, with an average night to day ratio of 0.87 for systolic blood pressure and 0.83 for diastolic blood pressure.[1] In some patients, the fall in blood pressure at night is blunted; a pattern referred to as non-dipping. Non-dipping patients may be at a higher risk of target organ damage.[24] Though diurnal variation, like variability and blood pressure load, may provide valuable information, an understanding of how this data can contribute to the management of hypertensive patients is still evolving.[18]

Cost-Effectiveness

Given the prevalence of hypertension and the large number of patients on antihypertensive therapy, the potential for the inappropriate use of ABPM is very large. This technology should not be used for the routine evaluation of all patients with suspected hypertension or monitoring therapy. Though it is relatively inexpensive ($50-$75), indiscriminate use may become an enormous cost to the health care system. Like all investigations, clinicians should think critically about why they are ordering this test and what new information it will provide.

When used appropriately, ABP can, in fact, be a cost-saving measure. ABPM can increase the cost-effectiveness of hypertensive treatment by differentiating between sustained hypertensives and white coat hypertensives.[25] The expense of testing is offset by the savings realized from not treating the large percentage of white coat hypertensives identified.[26]

Case Discussion

The principles of ABPM discussed will now be applied to the cases presented earlier, to outline how these patients were actually managed. Case 1 was that of a 53 year old male with mean of three clinic blood pressure readings of 145/90 and LVH on EKG. This patient was treated with antihypertensive medication because of the presence of target organ damage. ABPM would not have influenced management and was not indicated. Case 2 was that of a 72 year old female with a mean of three clinic blood pressure readings of 168/86 mm Hg and otherwise healthy. In this patient, with mild hypertension, no target organ damage, and no other cardiovascular risk factors, treatment depended on her actual blood pressure value. Being elderly and female, she was at particularly high risk for white coat hypertension. An ABPM was ordered and showed that this patient's mean 24 hour blood pressure was, in fact, 120/68 mm Hg with a daytime mean of 121/70 mm Hg. This is a striking example of marked white coat hypertension. She was reassured that her blood pressure was normal and no medication was prescribed. Case 3 was that of a 56 year old female on high dose acebutolol and enalapril and persistant clinic blood pressure readings of 158/94. ABPM was ordered in this patient to determine if her blood pressure medications should be increased. Her mean ABPM pressures were 110/68 mm Hg in 24 hours with a daytime mean of 114/71 mm Hg. It was decided to discontinue her enalapril and reduce her acebutolol dose from 800 mg/d to 600 mg/d. Clearly, the use of ABPM made a dramatic difference in the management approach.

Conclusions

Ambulatory blood pressure monitoring is an evolving technology with increasing popularity in the management of patients with suspected hypertension. Well validated devices are available that produce reliable estimates of 24 hr, daytime, and nighttime mean blood pressures. ABPM is of value in selected aspects of the diagnosis and management of hypertensive patients. Further research is needed to define a normal ABP and the prognostic significance of elevated mean ABP, blood pressure variability, load, and diurnal patterns. Such research is ongoing and may provide evidence for more extensive use of ABPM in the future.

Acknowledgements

The author would like to thank Drs. Gordon Hardacre, Jeff Bloom, and Barbara Stubbs by whom the patients discussed in this article were seen.

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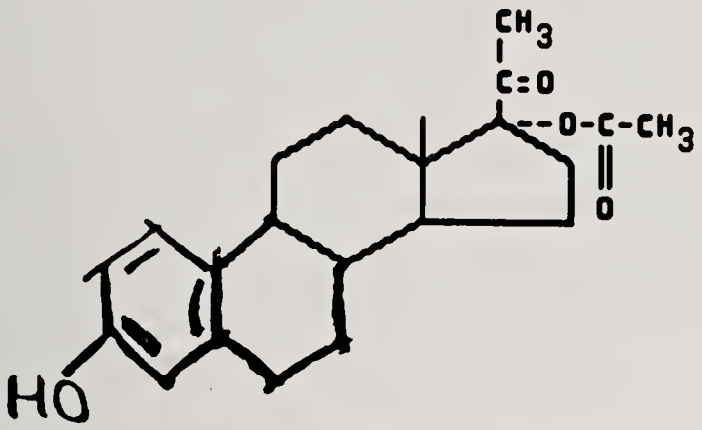

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Concomitant Hepatitis C Virus and Human Immunodeficiency Virus Infection: Two Major Players in a Complicated Disease Process

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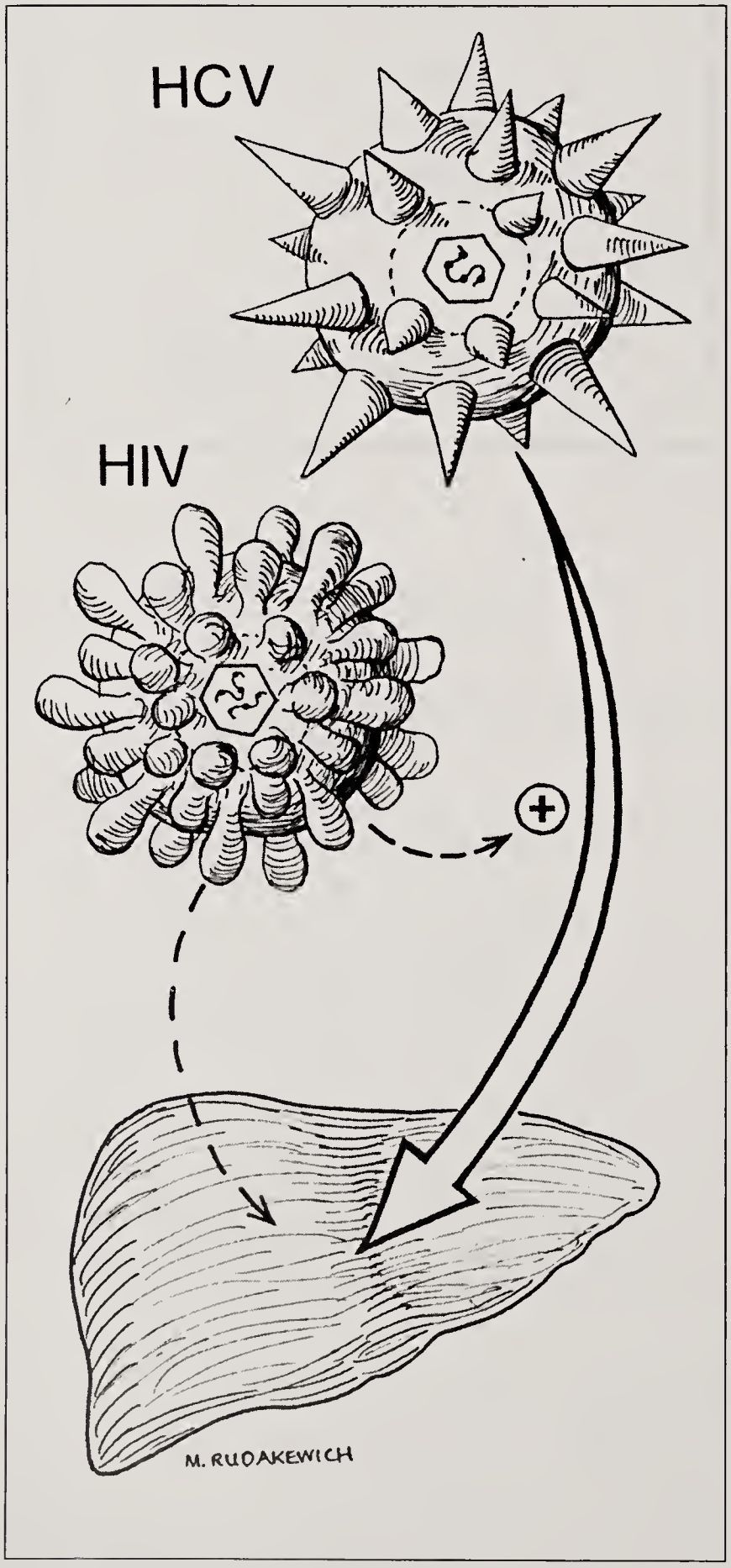

MYRA RUDAKEWICH

Abstract

The immunodeficient state that is induced by infection with the human immunodeficiency virus (HIV) has been shown to impact upon the natural history of hepatitis C virus (HCV) infection in individuals who are coinfected with both viruses. Coinfection has been associated with elevated levels of HCV replication and subsequent elevations in HCV viraemia, decreased HCV antibody (Ab) titres, and increased rates of progression to advanced liver disease.[1,2,3] Current clinical methods for detecting HCV infection rely on Ab-based second and third generation enzyme immunoassays (EIAs) with confirmatory recombinant immunoblot assays (RIBAs). These methods may inadequately detect HCV infection in immunocompromised HIV-infected individuals because of the associated decrease in HCV Ab titres that has been noted in dually infected individuals.[2] As such, it may be imperative that physicians not rely solely on HCV Ab tests in diagnosing HCV infection in HIV-infected individuals. It may be necessary to look directly for the presence of HCV nucleic acid (RNA) by polymerase chain reaction (PCR) to rule out HCV infection in the dually infected patient more confidently.

HCV Infection (without coincident HIV)

Seroprevalence and Transmission

The hepatitis C virus (HCV) was discovered in 1989.[4] It is the etiologic agent of most cases of what was formerly referred to as non-A, non-B hepatitis. It has been estimated from blood donor studies in Europe that the level of HCV infection in the general population is less than 1%.[5] Although the source of HCV infection is unidentified in up to one third of all infected patients, certain segments of the population have considerably higher rates of infection than are found in the general population. For example, the infection rates amongst hemophiliac and intravenous drug user (IVDU) cohorts have been reported to be as high as 50-90%. Dialysis patients who received blood products before blood screening for HCV was available in 1990 have also been shown to have higher rates of infection than the general population. The rate of infection amongst individuals who are sexually active with multiple partners, or with partners who are known to be HCV(+), has been shown to range between 3-15%, suggesting that HCV can be sexually transmitted.[6] Further evidence supporting possible sexual trans-

mission derives from the presence of HCV RNA in saliva, urine, and seminal fluid.[7] Vertical transmission has been shown to occur at a low frequency and is thought to be dependent on HCV viraemia during pregnancy and delivery.[8] The risk of transmission to healthcare workers is thought to be low. The seroconversion rate following a single needlestick injury from an HCV Ab(+) source is thought to be between 5-15%. Overall, 1.4% of healthcare workers are infected.[9] There remains, however, much debate over the transmissibility of HCV through occupational hazards. For example, one study found a higher incidence of HCV infection in dentists while another study found no difference in the incidence of HCV infection in dentists relative to the general blood donor population.[10,11]

HCV Pathobiology

The mechanisms by which HCV infection induces liver damage have not been fully delineated. The histological features most commonly associated with HCV infection include steatosis, intraportal lymphoid clusters, eosinophilic alteration of hepatocyte cytoplasm, and bile duct lesions.[12,13] The lymphocytic infiltration associated with HCV infection is not as prominent as the one associated with hepatitis B virus (HBV) infection.[12] These findings, together with the rapid decline in alanine aminotransferase (ALT) levels following interferon-alpha treatment, suggest a direct cytopathic effect of the virus.[12] Recent evidence such as the observation that ALT levels normalize during pregnancy (a state known to depress cell mediated immunity) and increase after delivery in most women with chronic HCV infection,[14] suggests that immune-mediated mechanisms may also play a role in the pathogenesis of HCV disease, although this role may be limited.[15]

Acute HCV infection is usually subclinical. Between 20-30% of patients may become symptomatic within 6 weeks and approximately half of these individuals may become jaundiced. Only very rarely is HCV the cause of fulminant hepatitis.[16] It is thought that at least 50% of acutely HCV-infected individuals progress to chronic HCV infection.[16] Positive correlative factors for progression to chronic infection include male gender, advanced age, HCV genotype, and a large initial inoculum of HCV.[17,18] Chronic HCV infection can manifest itself as chronic active (CAH) or chronic persistent (CPH) hepatitis. CAH may progress to cirrhosis and hepatocellular carcinoma over several decades while CPH is usually associated with a better prognosis.[16,19]

The high chronicity rate associated with HCV infection is suggestive of the virus' ability to evade host immune responses. This may be in part attributable to the fact that the virus has a large amount of genomic diversity, with six distinct genotypes having been defined. Although HCV has been shown to stimulate both humoral and cellular immunity, this immunity is thought to be weak.[20] It has also been shown that there is a lack of protective immunity against reinfection with homologous or heterologous viral strains.[21] These findings suggest that the high rate of chronic HCV infection may, in part, be related to an immune response that inadequately deals with HCV infection. No vaccine is currently available to prevent HCV infection.

Serum hepatic enzymes, such as alanine transaminase (ALT), are often used to follow the course of viral hepatitis, but may be extremely difficult to correlate with the severity of HCV infection. In acute HCV infection, they may be expressed as single peaks, alternatively, they may exist as plateaus, or their levels may fluctuate. In chronic HCV infection, ALT levels may be normal despite HCV RNA persistence.[22] Alternatively, they may fluctuate in what has been described as an "alpine" manner with repetitive peaks and troughs. One report has suggested that the cause of these fluctuations may be a result of the genetic "drift", which the virus is thought to undergo during chronic infection, allowing it to elude the host's immune response.[19] Some HCV Ab(+)/RNA(+) individuals have elevated ALT values while HCV Ab(+)/RNA(–) individuals do not, suggesting that increases in ALT associated with HCV infection are dependent on the HCV RNA status rather than the HCV Ab status in the infected individual.[23] Further studies are required to determine the validity of this proposition.

Diagnosis

Diagnostic tests currently available for detecting HCV infection include first, second, and third generation enzyme immunoassays (EIAs) and confirmatory recombinant immunoblot assays (RIBAs). These assays detect HCV antibody (Ab) and are indicative of previous exposure to the virus, however, they cannot distinguish an infection where the virus is actively replicating from one that has resolved. HCV PCR directly detects the presence of HCV RNA and can be used to determine whether a current infection is present. It is the most sensitive and specific test currently available to detect active HCV infection but unfortunately is only available in large testing centres.

Treatment

HCV infection can be treated with IFN-alpha for 6-12 months.[19,24] Up to 40% of HCV(+)/HIV(–) subjects respond to treatment by showing a disappearance of HCV RNA from their serum and liver. Unfortunately, 50-80% of the responders are likely to suffer relapse once the therapy is completed. Factors that have been shown to correlate with non-responsiveness include; high titre of HCV RNA, genotype, liver histology, age, male gender, and HIV seropositivity. It has been shown that steroid priming may increase responsiveness to IFN therapy. Furthermore, combination treatment with ribavarin, a nucleoside analogue that has been shown to inhibit other RNA viruses, may show superior results to treatment with IFN alone. There is only limited information on the role of interferon treatment in patients who are dually infected with HCV and HIV. HIV coinfection reduces the likelihood of successful treatment and this effect is thought to be related to CD4 (immunodeficiency) status.[25]

HCV and HIV Coinfection

Because HCV and HIV (human immunodeficiency virus) share common routes of transmission, it is not surprising that a significant number of HCV(+) individuals are found to be coinfected with HIV. The incidence of HCV infection in the HIV(+) patient population at The Toronto Hospital Immunodeficiency Clinic was found to be 11.1% overall with 70.8% of the clinic's IVDU population and 8.9% of the clinic's homosexual population being coinfected with HCV (unpublished data).

The exact nature of the effect of HIV coinfection on the natural course of HCV infection is yet to be determined conclusively. It is possible that the immunodeficiency state associated with HIV infection may induce a decreased humoral and cellular immune response to the presence of HCV. This could allow for enhanced HCV replication, which could result in an increased incidence of HCV chronicity, increased HCV viraemia and transmissibility, and a hastening of the progression to end-stage liver disease.

The Effect of Coinfection on HCV Ab Levels

There is convincing evidence that the immunodeficiency state associated with HIV infection decreases the anti-HCV humoral response and that this effect may be related to decreasing CD4 counts. There have been reports of HCV "sero-reversion" from an HCV Ab(+) to an HCV Ab(–) state despite persistence of HCV RNA in individuals with low CD4, suggesting that compromised immunity may be associated with loss of anti-HCV Ab response.[2,26] HIV(+) individuals with indeterminate (incompletely reactive) HCV RIBA results have been shown to have lower CD4 values than HIV(+) individuals with HCV(+) RIBA results[27] and high HIV viral load has been correlated with indeterminate HCV RIBA results.[28] These findings suggest that not only compromised immunity as determined by CD4 values, but HIV viraemia itself may be associated with the loss of anti-HCV Ab response. Further studies have shown that only rarely do HIV(–) individuals with indeterminate RIBA results have active HCV replication as determined by HCV RNA, while HIV(+) individuals with indeterminate RIBA results will be more likely to have active HCV replication.[29] The clinical implications of these studies indicate that HCV Ab tests may not be reliable in HIV(+) individuals as their immunodeficiency progresses. As such, HCV RNA tests should be used preferentially to rule out HCV infection in HIV (+) individuals with low CD4 values and clinical signs and symptoms suggestive of HCV infection.

The Effect of Coinfection on HCV Viral Load

Most studies indicate that the immunosuppression induced by HIV coinfection allows for enhanced HCV replication. For example, coinfected individuals have been shown to have an elevation of HCV RNA levels over time.[30,31] Several studies have found the percentage of patients with detectable HCV RNA to be greater in HIV(+) than in HIV(–) subjects.[32,33] Some authors have suggested that the level of viraemia can be correlated to the degree of immunodeficiency as reflected by CD4 status.[34] However, others have found that HCV RNA levels were not significantly associated with CD4 levels, concluding that the immunodeficiency state does not enhance HCV replication.[17,23] It may be that factors such as virulence of the different strains of HCV and their ability to evade host immune responses and replicate preferentially may account for these different findings. The clinical implications of the finding that HIV immunosuppression allows HCV to replicate at elevated levels implies that in HIV(+) individuals, transmission may be more likely because of higher viral loads, which may have significant implications on the course of HCV infection in the coinfected individual.

Liver Disease Markers (ALT) in HIV/HCV Coinfection

The evidence as to the effect that the immunodeficiency state associated with HIV infection has on HCV-induced liver damage or the progression to end-stage liver disease is conflicting. For example, several reports have shown that ALT levels are no different in HCV Ab(+)/HIV(+) individuals relative to HCV Ab(+)/HIV(-) individuals.[32] Others have shown that the number of HCV RNA(+)/HIV(+) individuals with elevated ALT relative to the number of HCV RNA(+)/HIV(–) individuals with elevated ALT is actually decreased.[23] What may account for these different findings is whether HCV Ab or HCV RNA was used as the marker for HCV infection since HCV Ab positivity may not indicate active infection while, HCV RNA positivity does. It was mentioned above that HCV may elicit its cytopathic effects directly on the liver.[12] The observation that there are fewer coinfected (HIV/HCV) individuals with elevated ALT values than there are in singly infected (HCV) individuals, indicates a stronger role for immune-mediated hepatic damage than is currently accepted. This finding is supported from other studies that have shown ALT levels to be depressed in non-HIV immunosuppressed individuals infected with HCV (drug induced following organ or bone marrow transplant, cytostatic treatment for haematologic malignancy, the pregnant state). Further studies are required to elucidate these findings. Furthermore, attempts should be made to correlate either CD4 values (reflective of underlying immune status), or HIV viral loads, with ALT profiles in coinfected individuals.

The Effect of Coinfection on Progression to Liver Disease

Studies conducted on HIV/HCV coinfected haemophiliacs have shown an increased rate of progression to end-stage liver disease relative to HIV(–) individuals with HCV infection.[33] Diammondstone[27] et al. suggested that insufficient HCV Ab responses because of HIV infection and immune dysfunction may account for the fatal liver disease in HCV(+)/HIV(+) individuals who had indeterminate HCV Ab results. They found the adjusted (age and CD4) mortality relative risk for individuals with indeterminate HCV Ab status to be 3.03 times greater than in those with a clear HCV Ab(+) status. Furthermore, they found that this difference increased over time as immune status declined. There is no unanimity in the literature, however, with regard to the effect of dual infection on the progression to liver disease, as some reports show that there is no difference in liver injury relative to individuals singly infected with HCV.[35] It is possible that since many of the studies investigating the role of coinfection on progression of liver disease were conducted in haemophiliac subjects, that the results may reflect a large initial HCV innoculum with repeated inoculations over time and/or different HCV genotypes as these individuals have mostly acquired their HCV infection through blood products generated from thousands of pooled donors. Hence, the more rapid progression to advanced liver disease seen in the coinfected individual may be related more to the total inoculum or genotype effect than to a coinfection effect. Further studies are needed to elucidate the role of dual infection on the progression of liver disease in coinfect-

ed individuals. These studies will have several methodological constraints since the livers of HIV-infected individuals are often compromised for reasons other than HCV infection. The livers of people living with HIV and AIDS can be affected by opportunistic infections, use of hepatotoxic medications, direct HIV infection of the liver,[36] or coinfection with hepatotropic viruses other than HCV (e.g., hepatitis viruses A, B, and D).

Future Directions

We are currently undertaking a retrospective cohort study at The Toronto Hospital Immunodeficiency Clinic investigating coinfection with HCV and HIV. The following factors are being characterized: risk factors for HCV transmission; correlates with HBV infection status; associations with relevant hepatic physical exam and investigational findings; and relationship between ALT values, HCV Ab status, HCV RNA status, CD4 values, and HIV viral load. Through such studies we hope to further characterize the complex relationship between HIV and HCV.

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Acute Cholecystitis: A Review of the Pathophysiology, Diagnosis, and Management

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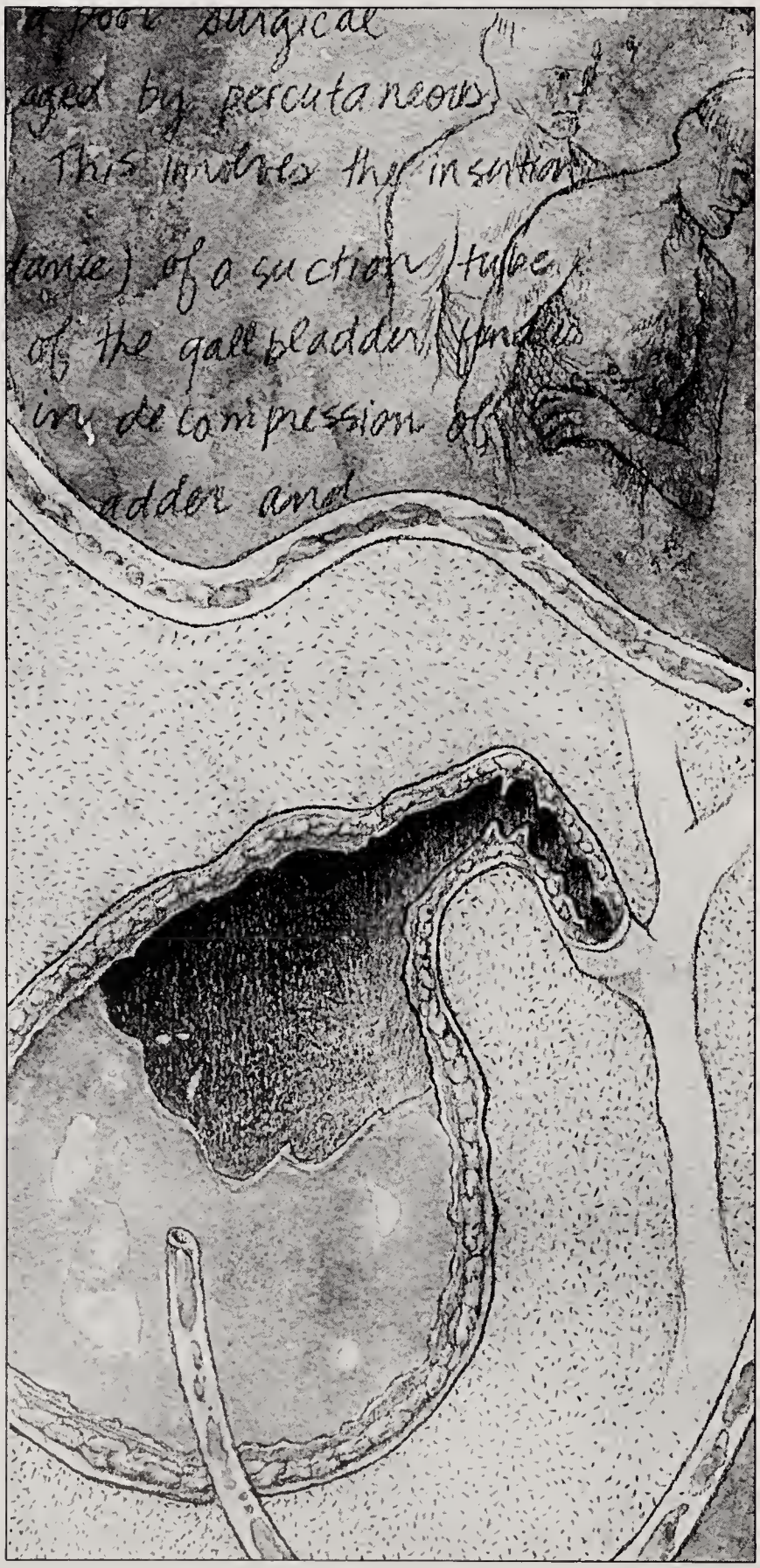

JENNIFER BOSY

Abstract

Acute cholecystitis is a condition that refers to inflammation and occasionally infection of the gallbladder. Patients with acute cholecystitis present with right upper quadrant or subcostal pain due to obstruction of the cystic duct or Hartmann's pouch by a gallstone. There are a number of ways of managing this condition. The best treatment is surgical removal of the gallbladder (cholecystectomy), by either open laparotomy or laparoscopically. For poor operative risk patients and for some cases of acalculous cholecystitis, cholecystostomy is often used. This paper reviews the pathophysiology, clinical presentation, and diagnosis of acute cholecystitis, and discusses the management of a case of acute cholecystitis by percutaneous cholecystostomy.

Introduction

One of the most common causes of the acute surgical abdomen is acute cholecystitis. It is characterized by distention and inflammation of the gallbladder. Acute cholecystitis may be associated with gallstones (calculous) or without (acalculous). Calculous cholecystitis accounts for the majority of cases; however, acalculous cholecystitis makes up a not insignificant proportion of cases, with some estimates being as high as 5-10%.[1-3] Risk factors for acalculous cholecystitis include burns,[4] trauma,[5] previous surgery,[6] and diabetes mellitus.[7]

Pathophysiology, Presentation, and Diagnosis

The pathogenesis of acute cholecystitis is complex and there are likely different etiological mechanisms based on whether stones are present.[8] Gallstone related cholecystitis likely develops after a stone obstructs the cystic duct, leading to secondary distention, ischemia, necrosis, inflammation, and infection of the gallbladder.[9] The pathogenesis of acalculous cholecystitis is controversial; however, it is likely that there are interactions between gallbladder ischemia, cystic duct obstruction, and concentration of bile.[8] Gallbladder distention in acute cholecystitis results in increased intraluminal gallbladder pressure, which can lead to gangrene and perforation of the gallbladder wall.[10] Infection of the gallbladder in

acute cholecystitis is most often caused by either *E. coli, Klebsiella,* or *Enterococcus faecalis.*[8] Some other organisms, however, have been isolated. These include *Pseudomonas,* some types of *Staphylococci, Enterobacter,* and anaerobes such as *Bacteroides* and *Clostridium.*[8] The pathological appearance of the gallbladder is similar in both calculous and acalculous cholecystitis. There is an infiltration of the fundal wall by acute inflammatory cells (polymorphonuclear leukocytes). In addition, edema and necrotic tissue may be found in the wall of the gallbladder.[11]

The common clinical presentation of acute cholecystitis of either type includes the sudden onset of right upper quadrant pain that often increases in severity.[9] As with simple biliary colic, this pain may also radiate to the right subscapular region. Other signs and symptoms include anorexia, nausea, vomiting, fever, and Murphy's sign (pain or inspiratory arrest elicited by subcostal palpation during deep inspiration).[9] Rarely, one may be able to palpate the gallbladder (Courvoisier's sign) (Table 1). Although the clinical features often point to gallbladder pathology, there are a number of other conditions that should be considered in the patient presenting with acute right upper quadrant pain, such as ascending cholangitis, pancreatitis, or peptic ulcer disease (Table 2). Acute cholecystitis can be a surgical emergency as complications such as emphysema, empyema, gangrene, or perforation of the gallbladder may lead to septic shock and death.[9] Importantly, these complications are more frequent in acalculous cholecystitis,[1,12] which accounts for its higher rate of mortality.[12] The development of these complications is often marked by high fever, increasing leukocytosis, or persisting or increased abdominal pain.[14] In addition, long-standing and neglected attacks of acute cholecystitis may lead to gallstone ileus due to gradual erosion of a large stone into the duodenum.

Table 1

Signs and Symptoms of Acute Cholecystitis

SIGNS	SYMPTOMS
Murphy's Sign	RUQ Pain
Courvoisier's Sign	Fever
Mild Jaundice	Nausea
Rebound Tenderness (with perforation)	Vomiting
Guarding	Anorexia

Table 2

Differential Diagnosis of Acute Right Upper Quadrant Pain

GASTROINTESTINAL	
acute cholecystitis	pancreatitis
chronic cholecystitis	gastro-esophageal reflux disease
ascending cholangitis	peptic ulcer disease
acute hepatitis	non-ulcerative dyspepsia
acute perforated gastric cancer	
CARDIOVASCULAR	
angina pectoris	acute myocardial infarction
abdominal aortic aneurysm rupture	ischemic bowel
GENITOURINARY	
renal or ureteric stones	renal infarct

Diagnosis of acute cholecystitis is often made clinically, but surgical intervention is usually not considered without the results of an abdominal ultrasound. The presence of gallstones or sludge along with gallbladder wall thickening and pericholecystic fluid, coupled with the clinical findings, is highly suggestive of acute cholecystitis.[15,16] It is important to note that the diagnosis of acalculous cholecystitis can be difficult to make because it often occurs in patients who are often critically ill for other reasons. As well, the ultrasound findings can be non specific. In these cases, HIDA scans (radionuclide scanning of the gallbladder following intravenous administration of a radiopharmaceutical) are useful.

The following case report illustrates the management of acute cholecystitis, which occurred following endoscopic retrograde cholangiopancreatography (ERCP) in a patient being investigated for obstructive jaundice.

Case Report

A seventy-five year old male, presented to an emergency department with severe right upper quadrant pain and fever of one week duration. He had undergone ERCP one week prior to the onset of his current symptoms.

One month prior to this admission, the patient presented to his family physician with a two month history of increasing jaundice and pruritus. He also had acholic stools and dark urine, all of which were consistent with biliary obstruction. The patient did not have a fever nor abdominal pain but did note a recent twenty to thirty pound weight loss despite normal appetite. The past medical history was only significant for a twenty year history of adult onset diabetes, which was being managed with oral hypoglycemic medications. On that occasion, physical examination revealed the patient to be deeply jaundiced. Abdominal examination was only significant for diffuse hepatomegaly. No masses were palpable. His initial laboratory studies showed total bilirubin to be elevated at 221 μmol/L (normal < 22). Aspartate transaminase and alkaline phosphatase were also elevated at 81 u/L (normal 10-40) and 337 u/L (normal < 125), respectively. A contrast enhanced CT scan of the abdomen demonstrated dilatation of both the intra- and extrahepatic bile ducts as well as a 2.5 cm stone in the gallbladder. There was no visible pancreatic mass. Despite the finding of cholelithiasis, there were no previous episodes of biliary colic or acute cholecystitis. An ERCP was performed where only the pancreatic duct was cannulated. It showed no abnormalities and the patient recovered

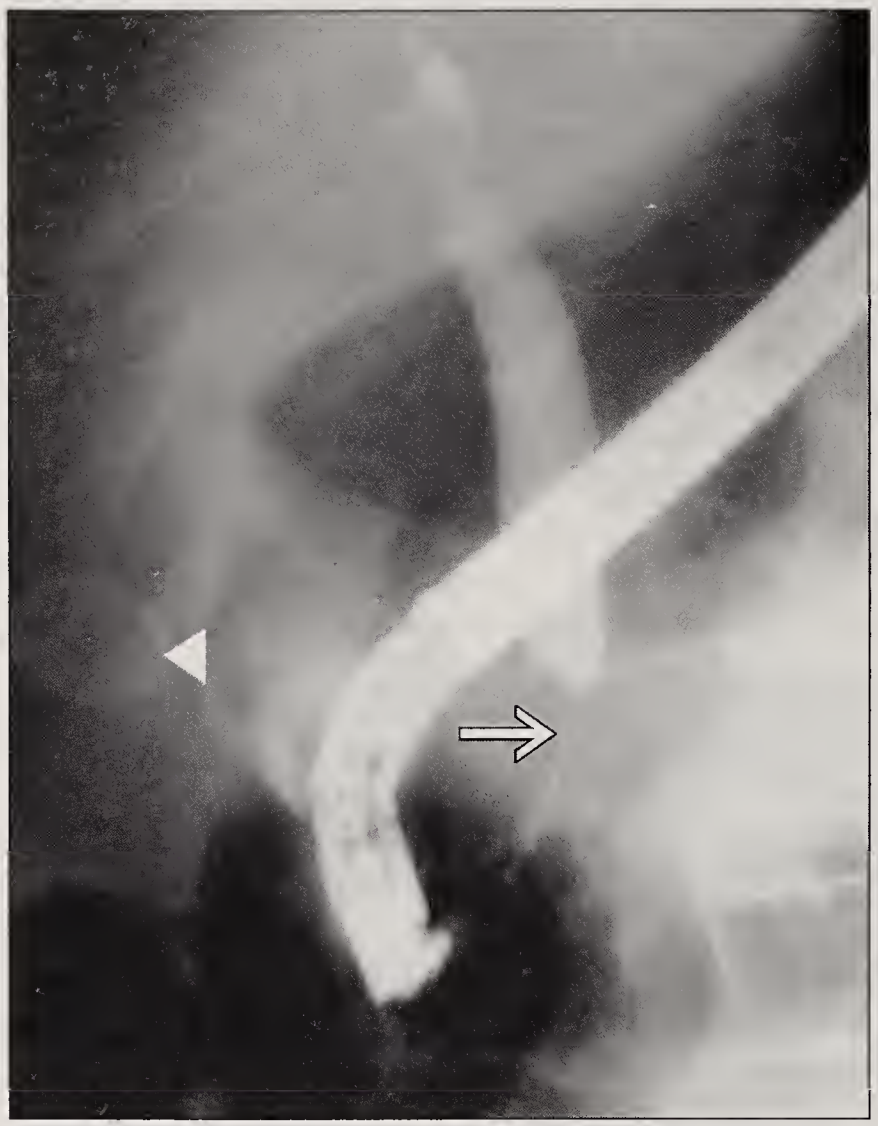

Figure 1: *ERCP (cholangiogram) image revealing tight stricture of distal common bile duct (arrow), dilatation of proximal bile duct, and a 2.5 cm stone in the gallbladder (arrowhead).*

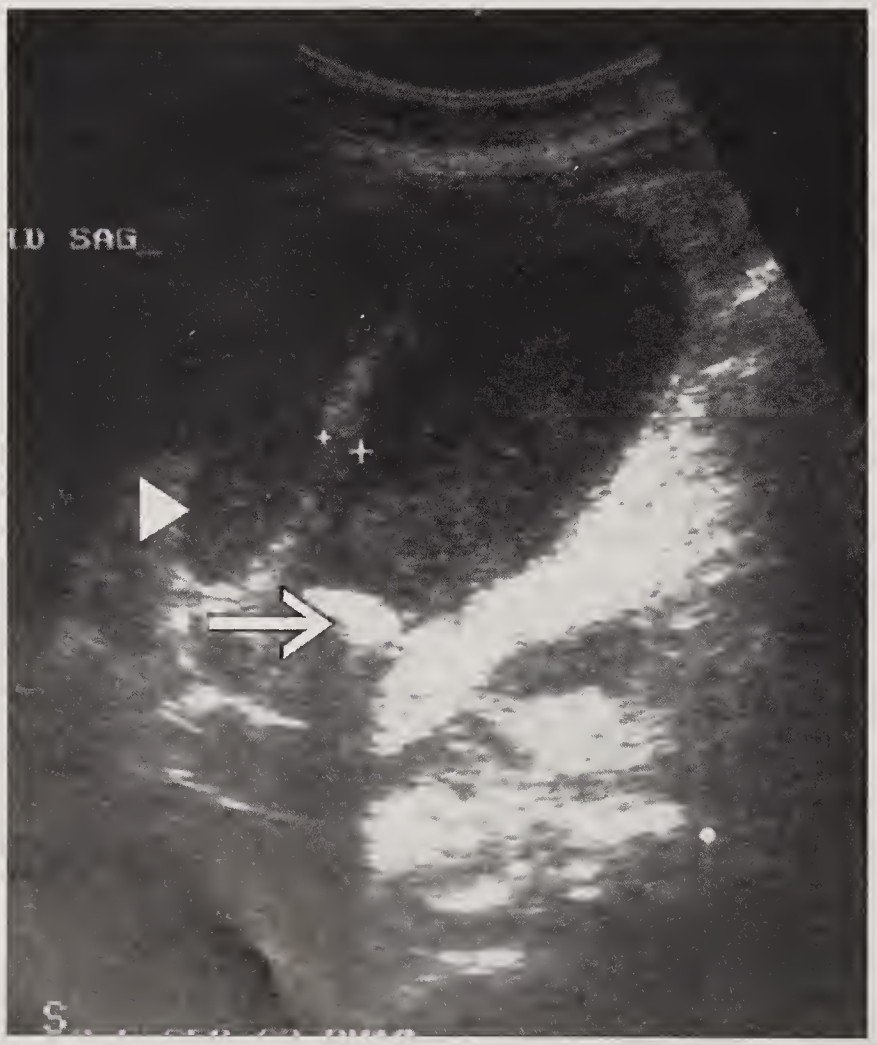

Figure 2: *Ultrasound image of the gallbladder showing thickening of the wall, sludge, pericholecystic fluid (arrowhead), and an impacted stone (arrow).*

uneventfully. A second ERCP was performed and a cholangiogram was obtained. This study revealed a tight stricture in the distal common bile duct with significant dilatation of the proximal biliary tree (Figure 1). A 5 cm long 10 French stent was placed to relieve the obstruction after endoscopic sphincterotomy. Since no pancreatic mass was evident, the diagnosis most consistent with the findings was cholangiocarcinoma. The patient was scheduled for a Whipple procedure (pancreaticoduodenectomy), but developed abdominal pain and fever approximately one week after his second ERCP. The pain was described as being constant and severe in the right upper quadrant. He said that his pain was worsening over the past week. The patient was admitted to hospital.

Physical exam revealed the patient to be febrile and in acute distress. Abdominal tenderness and guarding were localized to the right upper quadrant. There were no peritoneal signs and there was no increase in jaundice.

Laboratory studies did not reveal increasing biliary obstruction (total bilirubin 85 μmol/L and ALP 139 u/L). He however displayed a leukocytosis, with a total white blood cell count of 19.8 (normal 4-11). Most of these cells were neutrophils, indicating an acute inflammatory process. His hemoglobin was also low at 95 (normal 135-180).

An abdominal ultrasound (Figure 2) showed marked thickening of the gallbladder wall. Within the gallbladder lumen, an impacted stone, a large amount of sludge, as well as several sloughed membranes could be seen. In addition, there was a collection of fluid adjacent to the gallbladder fundus. These findings were consistent with acute cholecystitis and possible localized gallbladder perforation.

The patient was treated with broad spectrum antibiotics and ultrasound guided percutaneous cholecystostomy drainage. The procedure was tolerated well and the patient's symptoms disappeared shortly thereafter. A Whipple procedure was performed five weeks later and a pathological diagnosis of adenocarcinoma of the pancreas was made.

Management

There are three general methods in the treatment of acute cholecystitis. The choice depends on the condition of the patient and the progression of their illness. In addition, acalculous cholecystitis may be managed differently. In mild cases, especially in high risk patients, conservative nonoperative management is acceptable. This would involve the administration of antibiotics and intravenous fluids, as well as hospitalization to maintain NPO status.[9] Although patients treated in this manner may improve, their pain will often recur and they will eventually require surgery.[9] Moreover, progression of cholecystitis to gangrene and perforation is unpredictable.

Cholecystectomy is the mainstay of therapy[17,18] and should be performed within 24-48 hours of admission. The procedure can be done either laparoscopically or with an open laparotomy. The mortality rate associated with this procedure is variable. Rates vary from as low as 0.5% to as high as 7%, depending on the age and condition of the patient.[17,19,20]

If the health of the patient is good, removal of the gallbladder within 24-48 hours usually results in an excellent outcome.[21] In some cases where the patient presents a number of days after the onset of the acute illness, cholecystectomy may be delayed as long as the patient remains stable.[22,23] Cholecystectomy is occasionally very difficult if undertaken more than 48 hours after the onset of the inflammatory process. One must note, however, that if complications such as gallbladder perforation or empyema occur, emergency surgery must be performed.[24] Although acalculous cholecystitis may respond to other forms of therapy, calculous cholecystitis will virtually always ultimately require cholecystectomy.[25]

Patients who are poor surgical risk may be managed by percutaneous cholecystostomy. This involves the insertion (by ultrasound guidance) of a drainage tube into the lumen of the gallbladder fundus. Drainage results in removal of the infected bile, decompression of the distended gallbladder, and relief of symptoms. The risks of this procedure are lower than cholecystectomy. Many studies report no mortality associated with percutaneous cholecystostomy,[26] although there is some risk of having to undergo cholecystectomy if a necrotic gallbladder leaks bile into the abdomen around the cholecystostomy tube. Moreover, patients with cholecystostomy tubes often have moderately severe, chronic pain at the tube site and may eventually require cholecystectomy. The advantage of percutaneous cholecystostomy is that the patient does not have to be placed under a general anesthetic, which is important in patients with poor cardiac or respiratory function. As well, the procedure may be done at the bedside. This is an advantage in patients who are critically ill and develop acute cholecystitis while in the intensive care unit. In some cases, the gallbladder stones can be subsequently removed percutaneously through the cholecystostomy tube tract, thus avoiding cholecystectomy. This is especially useful in elderly, high risk patients. Cholecystostomy is also useful when the surgeon wishes to delay the cholecystectomy for medical or practical reasons as in the present case. In cases of acalculous cholecystitis, percutaneous cholecystostomy has been shown to be definitive therapy, with little to no risk of having to undergo subsequent cholecystectomy.[7,25,26,27]

Summary

The patient discussed above presented with the clinical signs and symptoms of acute cholecystitis one week following ERCP, a well recognized but uncommon and poorly understood complication.[28] The patient was scheduled to undergo a Whipple procedure, which includes removal of the gallbladder. If the patient had been managed by cholecystectomy at the time of his acute cholecystitis, it would have significantly complicated the forthcoming Whipple operation. It was therefore decided that the patient be managed by percutaneous cholecystostomy. This relieved the patient's symptoms and obviated the need for urgent cholecystectomy. This case demonstrates the usefullness of percutaneous cholecystostomy for treating selected patients with acute cholecystitis when immediate surgery is either dangerous or undesirable.

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Iliac Artery Stenosis: A Case Report Illustrating CT Angiography, Intravascular Ultrasound and Arterial Stenting

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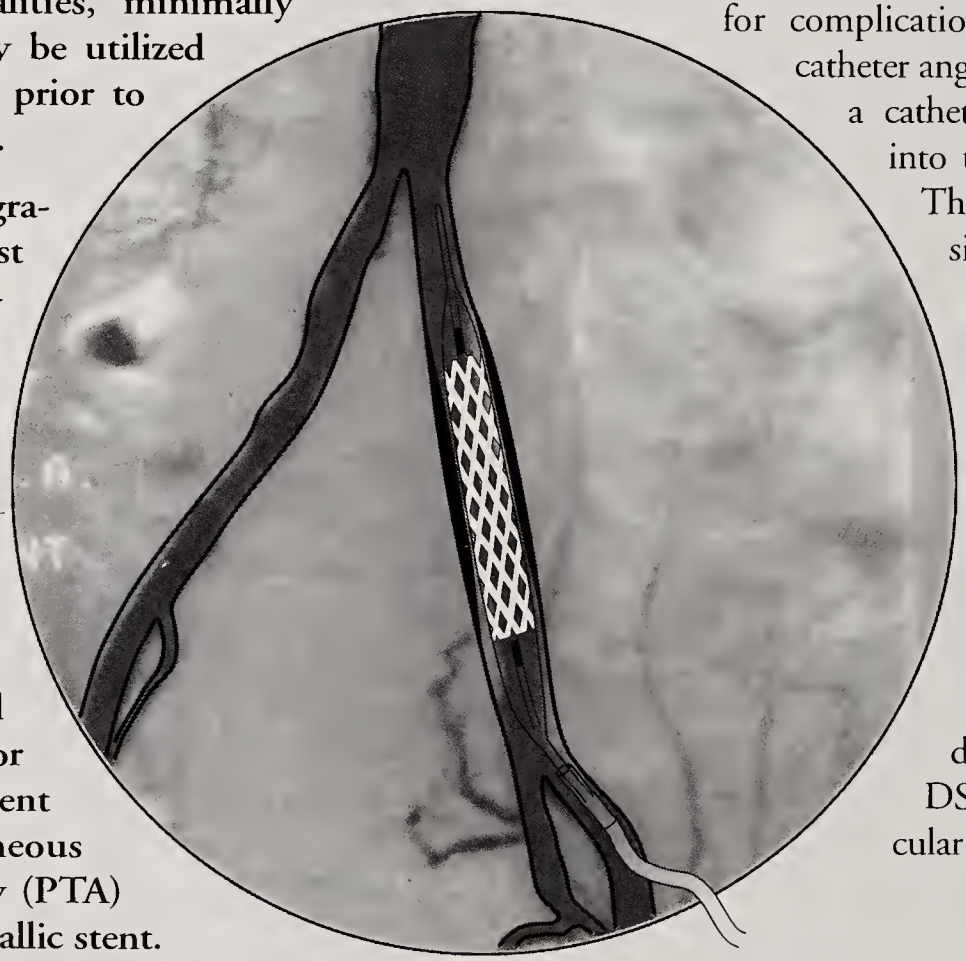
Abstract

In this case report we describe some of the recent advances in diagnostic and therapeutic imaging as applied to the investigation and treatment of peripheral vascular disease (PVD). As a result of more specialized imaging modalities, minimally invasive techniques may be utilized for diagnostic purposes prior to therapeutic intervention.

In this case, CT angiography (CTA) was the first imaging study performed, confirming the clinical diagnosis of left common iliac artery stenosis. Subsequent digital subtraction angiography (DSA) and intravascular ultrasound (IVUS) confirmed and localized the lesion prior to angioplasty. Treatment consisted of percutaneous transluminal angioplasty (PTA) with placement of a metallic stent.



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Introduction

Peripheral vascular disease (PVD) is a problem that affects 8.0% to 11.7%[1,2] of the general population. While there are a number of non-invasive tests for investigation and diagnosis of PVD, conventional angiography remains the gold standard. The development of spiral CT has allowed for three dimensional, angiogram-like images to be created from the data from a peripheral venous contrast injection. This technique, known as CT angiography (CTA), has been found to be a safe, noninvasive way to evaluate a wide variety of vascular abnormalities.[3,4] The gold standard vascular imaging modality remains the angiogram. Modern computer and software has allowed for the development of Digital Subtraction Angiography (DSA). This technique is faster and requires less contrast and radiation in comparison with standard film x-ray techniques. However, this is an invasive modality with some pitfalls and the potential for complication. A recent advance in catheter angiography is the placement of a catheter based ultrasound probe into the vascular system (IVUS). This is a very sensitive, but invasive method to accurately evaluate the vessel wall. Balloon Angioplasty (PTA) was developed over 30 years ago. In addition to technical refinements in the basic procedure, the placement of metallic stents into the vessels is now becoming common. We describe a case which demonstrates the use of CTA, DSA, IVUS, PTA and intravascular metallic stenting.

Case

A 56 year old man presented with recent onset of intermittent claudication of his left leg. He was referred to a vascular surgeon with the complaint that he could walk for only 3 to 4 minutes without resting. On physical examination, a bruit was noted over his left femoral artery, the left femoral pulse was weak and distal pulses of the left lower extremity were absent. The remainder of the physical examination was unremarkable. The ankle-brachial index (ABI) was 0.71 on the left, indicating significant stenosis. From the clinical examination, the stenosis was suspected to lie within the left iliac artery, and to confirm this, he was referred to radiology for further investigation.

Spiral CT (CTtwin, Elscint, Haifa, Israel) using CTA technique[3,4] demonstrated a long, significant, calcified stenosis of the left common iliac artery (Figure 1a, 1b), and the patient was referred for PTA.

Arterial access was achieved using ultrasound guidance to puncture the non-palpable left common femoral artery. Following placement of a 9 French (F) vascular sheath, DSA was performed with a 5F pigtail catheter and IVUS was done using an 8F catheter based transducer (Aloka model 55D 2000, Tokyo) (Figure 2a,2b). Both DSA and IVUS confirmed the CTA findings of significant stenosis. PTA was performed using a 10 mm diameter balloon, However, the post PTA angiogram demonstrated moderate residual stenosis. To overcome the elastic recoil, a 10 mm diameter, 68 mm length Wallstent (Schneider,Guelph, Ontario) was placed across the lesion. Follow-up angiography demonstrated a widely patent vessel with no evidence of stenosis or dissection (Figure 3). Repeat IVUS confirmed

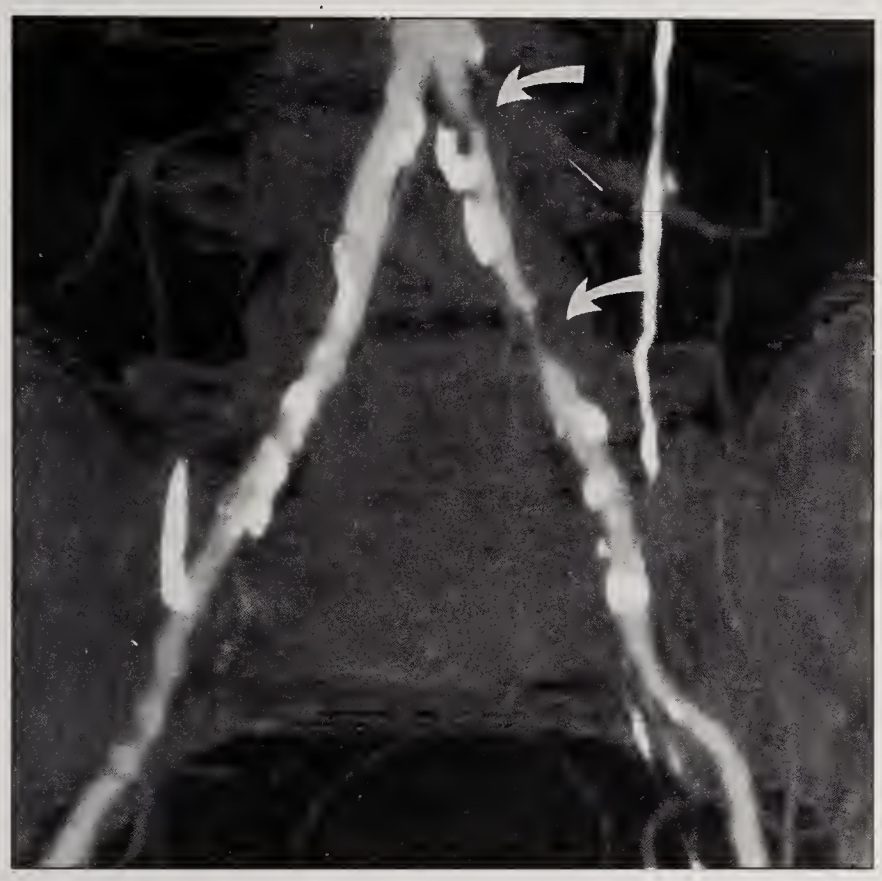

Figure 1a: *Maximal Intensity Projection image demonstrates moderate calcified plaque involving both iliac arteries. There are 2 focal short significant stenoses on the left (arrows).*

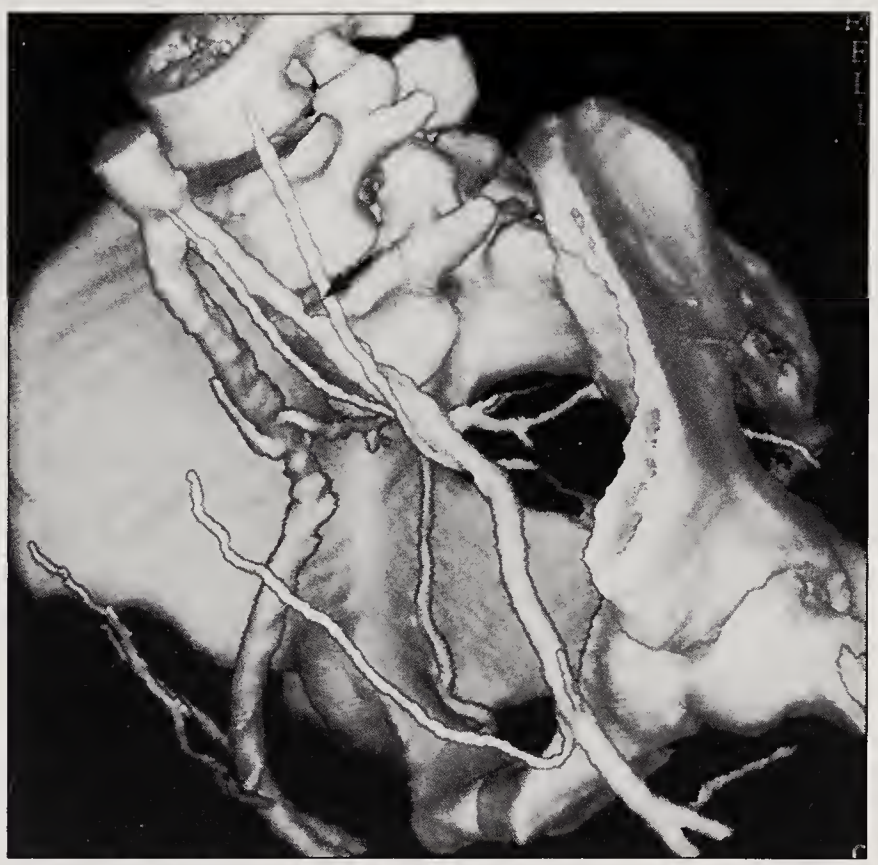

Figure 1b: *The left common iliac artery appears diffusely narrow with a single short significant stenosis (arrow) on oblique Shaded Surface Display.*

Figure 2a: *Frontal view from intra arterial angiogram shows a single short significant stenosis in the distal left common iliac artery (arrow).*

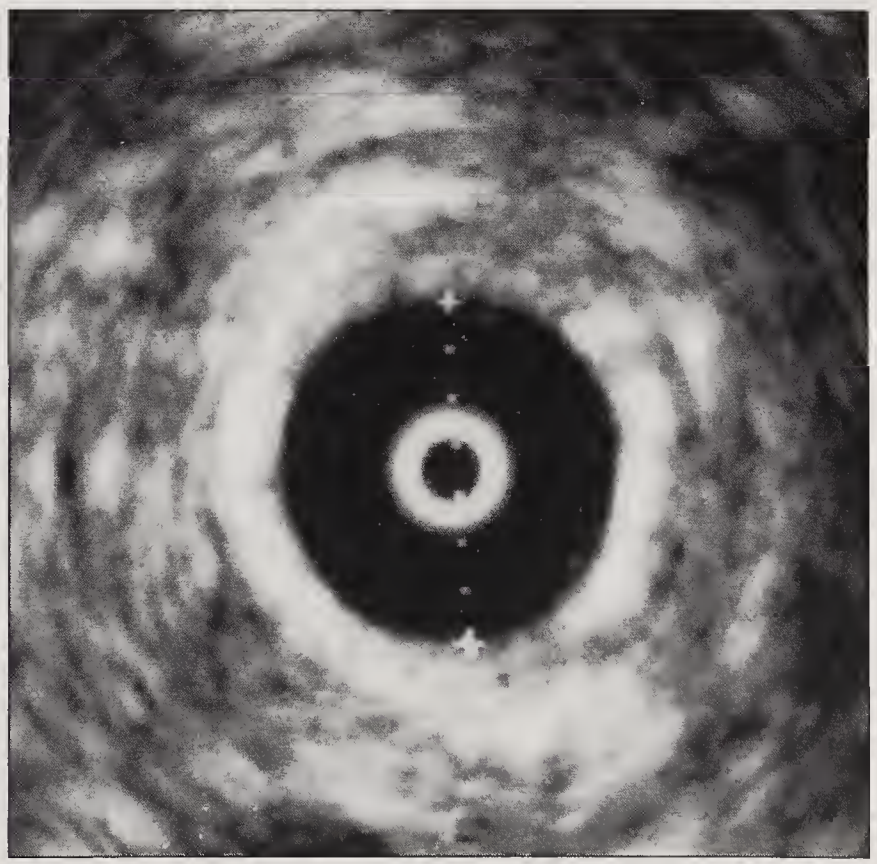

Figure 2b: *Intravascular U/S image shows the probe occupying the entire vessel lumen. Calipers demonstrate the limits of the probe within its sheath.*

good position of the stent with its proximal tip extending just into the aorta (Figure 4).

The patient tolerated the procedure well, having received only intravenous sedation and local anesthetic. He was observed overnight and was discharged the following morning on dipyridamole. At 2 month follow-up, his exercise tolerance had significantly improved. The left sided ABI was 1.15, and his left lower extremity pulses were normal to palpation.

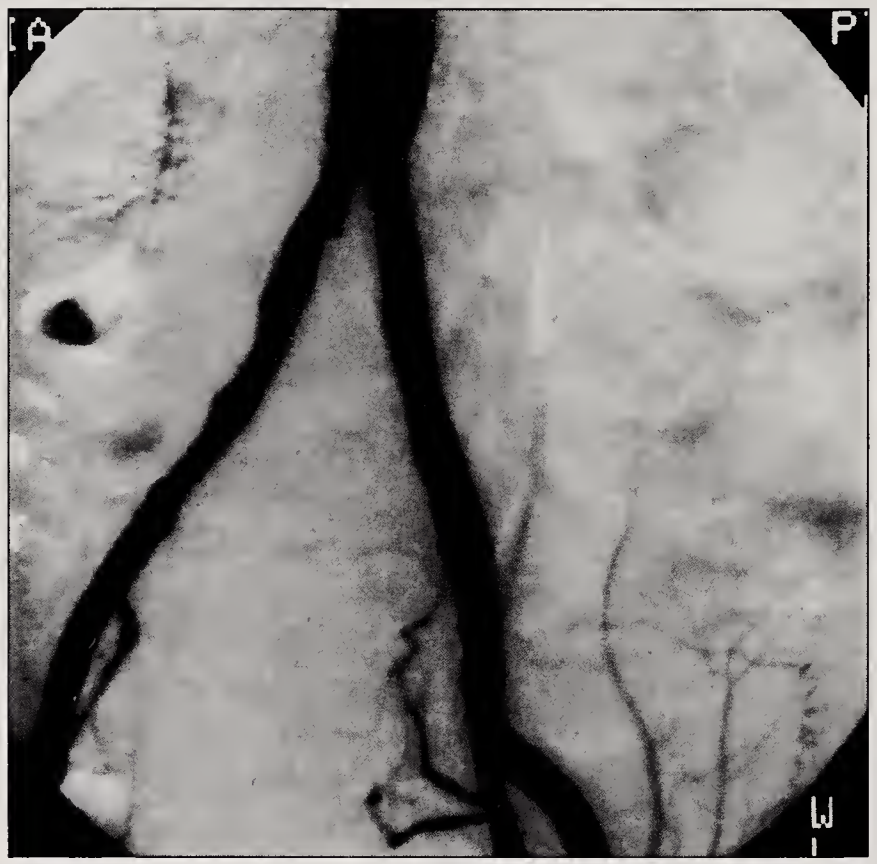

Figure 3: *DSA image post left PTA and stent placement shows near anatomical result.*

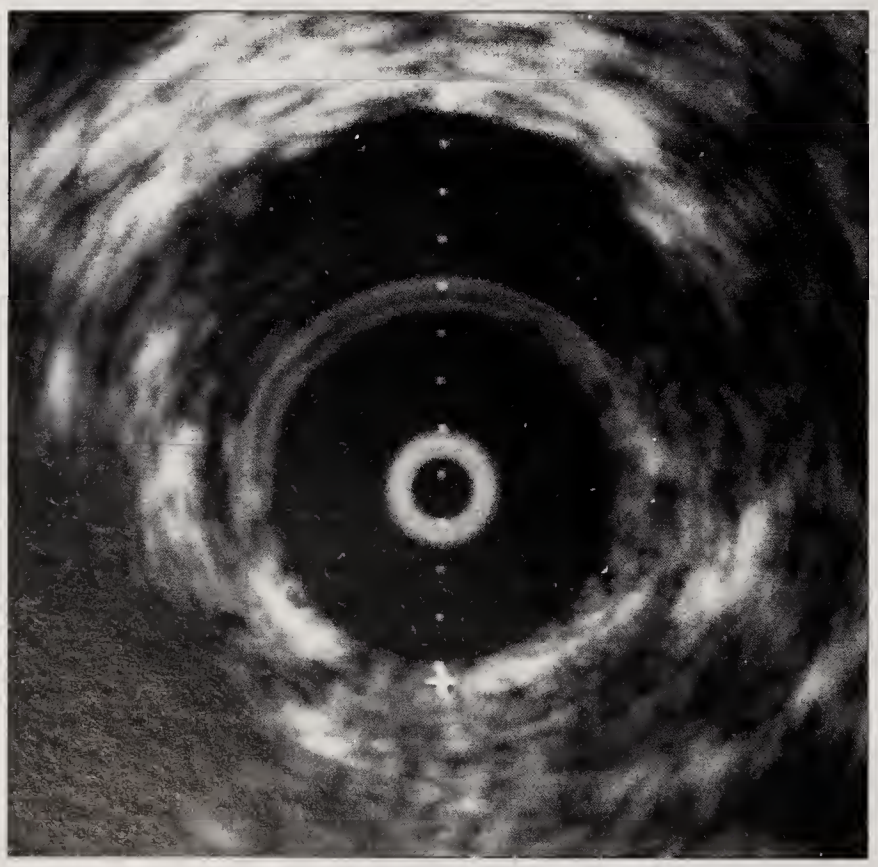

Figure 4: *Intravascular U/S image (obtained at the same location as image 2b) post PTA and stent placement shows the lumen to be 10 mm in diameter. Calipers demonstrate the extent of the lumen.*

Discussion

Previously, conventional angiography or DSA have been the initial diagnostic tests performed on patients with signs and symptoms suggestive of peripheral vascular disease. Although some feel that both diagnostic and therapeutic interventions can take place during a single procedure, most interventional radiologists believe that the therapeutic procedure should be performed separately, after the investigation is reviewed and the appropriate access and time for the intervention is planned. CTA allows for accurate assessment of the vascular system noninvasively to allow for this planning.

The development of spiral CT technology and its ability to acquire a volume data set during the arterial phase of an intravenously (IV) administered contrast bolus has allowed for development of CTA.[3,4] Spiral CT utilizes a slip ring coupling which allows for continuous rotation of the x-ray tube (and detector) with continuous movement of the gantry through the x-ray tube, resulting in data acquisition that was not available through previous CT technology.[5] Using this technique, a data set representing a volume of tissue may be obtained with post processing editing allowing for the creation of a three dimensional rendition of the vascular tree. Since there is only a standard IV injection, there is no post procedure recovery and an insignificant rate of complication compared to conventional angiography.[6] The complications of arterial access such as haematoma, obstruction and dissection are completely eliminated.[7] The two main types of CTA images are the Shaded Surface Display (SSD) and the Maximum Intensity Projection (MIP). SSD images depict the outside of the vessel (the wax mold) whereas MIP images are necessary to demonstrate complex calcified lesions.

Another advance in the investigation of arterial disease has been the miniaturization of ultrasound transducers allowing for their introduction into the intact vessel lumen. Intravascular ultrasound transducers can be mounted on catheters smaller than 10 F, allowing accurate measurement and characterization of arterial lesions. In addition, more accurate balloon or stent size selection is possible.[8,9]

Technical aspects and success rates of PTA continues to improve since its development in 1964.[10] The primary patency rate of PTA for iliac stenosis has been recognized by various authors as 67-95%.[10-12] Vascular stenting is another innovation, with the first human implants placed in 1987.[13,14] With the development of new materials and deployment mechanisms, vascular stenting has now achieved relative success.[15] Although vascular stents were initially reserved for use in cases of failed angioplasty, some authors prefer primary placement of arterial stents.[15,16] Several randomized controlled trials are underway to develop a more evidence based algorithm for stent placement. Technical success rate of arterial Wallstent placement in the iliac arteries has been extensively studied, with primary patency rates reported as 97-100%.[14,16,17] Patency has been reported to be 87- 93% at 6 months, which is comparable to angioplasty and vascular surgery.[14,17,18]

This case represents a nice pictorial example of a number of recent innovations in interventional radiology. CTA allows

accurate noninvasive diagnosis of vascular diseases while IVUS is an invasive way to very accurately examine the vessel wall. Metallic stents have been found to be a valuable adjunct to standard angioplasty.

Acknowledgment

We would like to thank Guglielmina Picano for her assistance in preparing this manuscript.

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Death Investigation In Ontario

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The *Coroners Act* of Ontario legislates the reporting to and investigation of certain types of deaths by physicians who are appointed as "Coroners".

Once a death is reported to a coroner, the coroner has a duty to identify the deceased, and to determine the facts as to how, when, where, and by what means death occurred. Section 10 of the *Coroners Act* of Ontario lists the types of deaths that must be reported to a coroner by – everybody who has reason to believe that the deceased person died:

- as a result of:
  - i) violence,
  - ii) misadventure,
  - iii) negligence,
  - iv) misconduct, or
  - v) malpractice
- by unfair means
- during pregnancy or following pregnancy
- suddenly and unexpectedly
- from any disease or sickness for which he/she was not treated by a legally qualified medical practitioner
- from any cause other than disease, or
- under any circumstance that requires investigation.

Once a death has been reported, the *Coroners Act* directs that no person shall interfere with or alter the body or its condition in any way without the direction of the Coroner.

The *Coroners Act* also lists a number of institutions, such as Homes for the Aged, Nursing Homes, Children's Residences that must report every death. The manner of reporting is detailed in the legislation.

Once a coroner has been notified about the death, the coroner has the authority to determine whether or not an autopsy will take place. Consent from the family is not required. There are circumstances where the family's wishes may be important to the coroner in making the determination about the nature of medical-legal autopsy. Anyone who has knowledge of the wishes of the family should report those wishes to the investigating coroner in order that they can be considered.

The coroner has wide authority to carry out his/her investigation. A coroner may view and take possession of any dead body, may enter and inspect any place where the dead body is or any place from which the coroner believes the body was removed. A coroner may, where he/she believes on reasonable and probable grounds; inspect any place in which the deceased person was, or which the deceased person was prior to death; to inspect and extract information from any records or writings that relate to the deceased; and, seize anything that the coroner has reasonable grounds to believe is material to the purpose of investigation.

Other agencies assist coroners in the investigation of death. The Centre of Forensic Sciences is a leading crime lab and is of great assistance in determining the cause of death with respect to examination of body fluids. The coroner also often calls on the investigative ability of the Office of the Fire Marshal and the Ministry of Labour.

The *Coroners Act* requires that the police service in the area where the death occurred provide assistance to the coroner in the investigation if requested. It may be that a person with information concerning the circumstances of a death may be approached by a police officer acting on behalf of a coroner.

There are approximately 400 coroners throughout the province of Ontario. The province is divided into eight regions and for each region a full time Regional Coroner manages the activities of the coroners within the area. There are two Deputy Chief Coroners in the Office of the Chief Coroner. One Deputy Chief Coroner is responsible for monitoring the investigations of the Province. The second Deputy Chief Coroner is responsible for coordinating inquests that are held throughout the Province. A Chief Forensic Pathologist coordinates forensic pathology in the province and advises the Chief Coroner on this aspect of death investigation.

The motto of the Office of the Chief Coroner is "we speak for the dead to protect the living". The intent of the motto is to determine the circumstances of deaths and secondly, to assess those circumstances with respect to prevention of similar deaths in the future. There are a number of ways that an investigating coroner can achieve that end.

The coroner may discuss the circumstances with the involved individuals and suggest changes that might have prevented the death.

Alternatively, the coroner may recommend a Regional Coroner review which is a meeting convened by the managing coroner of the area to discuss the circumstances. There are four expert committees that assist the Office of the Chief Coroner in reviewing deaths in specialties such as Obstetrics, Paediatrics, Anaesthesia, and Geriatric and Long Term Care. Often these committees have recommendations that can be communicated at a Regional Coroner's Review. If the recommendations are felt to be appropriate, they are implemented by local hospital administration and medical or nursing staff.

The third opportunity to effect change and hopefully therefore to prevent deaths in similar circumstances is the convening of a coroner's inquest. The *Coroners Act* of Ontario legislates mandatory inquests in certain types of deaths such as those that occur as a result of an accident on a construction site, mining pit or quarry or deaths that occur in custody.

An inquest jury is entitled to answer the five questions: who, how, when, where, and by what means death occurred and to hopefully make recommendations that might prevent deaths in similar circumstances. Jury members are allowed/encouraged to ask questions of witnesses at an inquest. A jury is prohibited by the *Coroners Act* from making any finding that either states or implies blame or legal responsibility. The inquest therefore is truly a fact finding inquiry with the intent of identifying any public safety issues.

Information concerning a coroner's investigation can be obtained by the family. Anyone other than the family may obtain the information only with the consent of the legal next of kin. If an autopsy is conducted on a patient who dies in a hospital, a copy of the autopsy report may be released to the hospital medical record department. There are times when this release will depend on certain court proceedings and it must be released only after appropriate consideration by the investigating coroner.

Further information concerning obligation to report deaths in the Province or other questions concerning the conduct of a coroner's investigation may be addressed to the Office of the Chief Coroner. The Office is located in Toronto at 26 Grenville Street and the phone number is (416) 314-4000.

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Case Records of The University of Toronto Medical School

Clinicopathological Exercises

Founded by Frank V. Ritacca, David J. Klein and Michael S. Pollanen

Robert Yu, Editor

This Clinicopathological Conference was held at the Toronto Hospital (Western Division) on December 12, 1996.

Presentation of Case

A 20 year old woman was brought to an emergency room with somnolence. In the previous 48 hours, she had presented to the same hospital on three separate occasions. On the first occasion, she complained of urinary retention. A diagnosis of urinary tract infection (UTI) was made and she was sent home. On the second presentation, she complained of the same symptoms but her urinary retention necessitated catheterization and she was febrile. She was eventually discharged. On the third occasion, her reduced level of consciousness was associated with nausea, incoherent speech, headache, confusion, and "difficulties walking".

Past medical history was significant for asthma and a poorly delineated psychiatric history, with two suicide attempts by drug overdose (sertraline and acetominophen). Over the past week, she had treated a "flu-like" illness with "over the counter" medications.

On initial physical examination, she was disoriented (x3), pupillary light responses were normal, fundoscopic examination was unremarkable, and limb reflexes were symmetrical (2+), with downgoing toes. Her neurological status changed rapidly in hospital over the course of hours. Her lower limbs became areflexic and flaccid, while her arms maintained symmetrical reflexes (2+). She did not respond to verbal commands or move limbs spontaneously, but did respond to deep pain stimuli. The left pupillary light response was brisk and the right was sluggish.

The initial chemistry consisted of a complete blood count, liver function tests, arterial blood gases, BUN, creatinine, electrolytes, and other ions. All values were unremarkable. There was no increase in the anion gap. A drug screen was negative. Urinalysis and culture were non-contributory. A CT scan of the head did not reveal any abnormalities. A lumbar puncture was performed (opening pressure - 26cm of water). The CSF protein was 0.9 g/L and the white blood cells were 0.022 x 10^9 cells/L with 74% lymphocytes. She was transferred to a University of Toronto teaching hospital after one day in the hospital with a Glascow Coma Scale of 3-4.

On arrival to the teaching hospital, her respiratory status was poor and she was intubated. Her general status was essentially unchanged, however, there was now hyporeflexia of the upper limbs. A repeat lumbar puncture gave a similar biochemical and cellular profile with 88% lymphocytes. Polymerase chain reaction (PCR) of the CSF for Herpes Simplex Virus (HSV) was negative. MRI scan revealed multiple subtle foci of increased signal intensity in the right caudate nucleus and putamen, with diffuse increased signal in the cervical spinal cord from C2-C7.

Her neurological status remained unchanged for ten days in hospital. On the tenth day, there was response to verbal stimuli but the quadraparesis was still present. The course in hospital was complicated by multiple medical problems including episodes of sepsis (UTI, transiently positive blood cultures for *Staphylococcus aureus*), problems related to the placement of the endotracheal tube, and episodes of nocturnal apnea.

On day 17 in hospital, the Glascow Coma Scale was 10. However, the quadraparesis was unchanged, and she remained vetilator dependent. Over the next two weeks, her neurological status did not improve and on day 31, a feeding tube was inserted. On day 34 in hospital, a tracheotomy was performed to insert a tracheal tube for continued respirator dependence. However, the patient died suddenly during the procedure. An autopsy was performed.

Differential Diagnosis

Warren P. Mason, M.D., F.R.C.P.(C.)
Staff Neurologist, The Toronto Hospital
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I will begin the discussion of this case with a differential diagnosis of urinary retention as this was her initial presentation. Upon admission, a provisional diagnosis of urinary tract infection was made, which is unusual for a patient that presents with difficulty voiding requiring catheterization.

In terms of neurological explanations for urinary retention or bladder dysfunction, there are a number of entities to be considered including sensory-motor neuropathy involving sacral nerves. This can occur from trauma to the lumbosacral region that damages the cauda equina or causes disk prolapse. In addition, a demyelinating polyneuropathy such as Guillain-Barré Syndrome can present with bladder abnormalities. An interesting viral infection that is probably underrecognized and underdiagnosed is herpes zoster of sacral nerves. There have been reports of series of patients who present with bowel and bladder incontinence, who do not have pain, and do not have rash typical of herpes zoster. Cauda equina tumors such as ependymomas or schwanommas can sometimes present with bladder dysfunction. Diabetes mellitus can result in a neuropathy that is autonomic or sensory motor and can give bladder dysfunction. Other autonomic neuropathies such as Shy-Drager syndrome, must also be considered in this case. Recently, increasing work on sphincter control or co-ordination abnormalities have been reported as explanations for bladder dysfunction. Entities such as bladder neck spasm can be implicated as a chronic cause of urinary dysfunction. Most importantly, in this case, the last cluster of diagnoses that must be considered are spinal cord lesions from either infarction of the conus medullaris or the spinal cord, myelitis, or spinal shock from a variety of causes.

As the case unfolded, in addition to the urinary retention, the patient developed other neurological symptoms and signs, that modified the differential. She had hyporeflexia, hypotonicity of the lower legs, sluggish pupils, and became encephalopathic. These findings suggest involvement of the CNS more generally including the conus medullaris and spinal cord. This is also supported by the lymphocytic infiltration in the CSF. Viral causes for this presentation need to be considered, and there is not enough evidence to exclude agents such as cytomegalovirus (CMV) and herpes zoster, although PCR of the CSF was negative for herpes simplex virus.

Demyelination is also a strong possibility. The evolution of the clinical findings is consistent with central nervous system demyelination. In addition, one also needs to consider a systemic vasculitis with CNS involvement. A number of conditions, such as Churgg-Strauss syndrome, systemic lupus erythematosus (SLE), rheumatoid arthritis, or isolated CNS angiitis, may present with this picture.

The differential diagnosis can be modified further by the MRI abnormalities that were uncovered from the initial and subsequent scans. May we now review the imaging studies?

Radiological Discussion

Two MRI studies of the brain and spine were performed, once early in the admission, and the second seventeen days later. The abnormalities are fairly subtle. Initially there was some question of an abnormal signal in the pons. There was also abnormal signals close to the internal capsule and the deep grey nuclei. In addition, there was a vague abnormal signal in the head of the caudate on the right.

There was an indefinite area of increased signal in the lower medulla and in the spinal cord at the C2 level. One gets the impression of a very subtle diffuse signal abnormality down to C7 in the cervical cord. As well, the cord may have been slightly swollen. Seventeen days later, there was a poorly defined but fairly diffuse abnormality in the medulla consisting of a hyperintense signal. There was no breakdown of the blood-brain barrier with gadolinium.

Differential Diagnosis Continued

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Staff Neurologist, The Toronto Hospital
Faculty of Medicine, University of Toronto

The MRI abnormalities explain the critical findings that were persistent in this patient including coma, pupillary abnormalities, and ventilator dependence, which led ultimately to death. Putting this together, the differential diagnosis can now be reduced to a much smaller group of disorders including: viral infection, vasculitis, CNS neoplasms (the most important that must be excluded is CNS lymphoma), and CNS demyelination (either acute presentation of multiple sclerosis like illness or acute disseminated encephalomyelitis). I will now discuss each of these group of diseases.

The viral infections that are important to consider include herpes zoster, CMV, and herpes simplex virus. Herpes zoster is more common in the elderly or the immunocompromised, and dissemination would be necessary to present in this fashion. This would be very rare. Importantly, delayed neurological deficit can occur secondary to herpes zoster vasculitis. The vasculitis here usually follows the initial presentation by weeks to months, not acutely as in this case. The mortality is extremely high (up to 25%). HSV can be excluded quite easily by the fact that the PCR results were negative and the MRI findings were not characteristic of herpes simplex encephalitis. In HSV encephalitis, there is usually a temporal-frontal distribution of disease, which was not seen here. Lastly, CMV cauda equina syndrome is well described, particularly in patients with AIDS. We have no evidence that this woman was HIV positive, although no tests were done.

The patient's presentation and some of her MRI findings are entirely consistent with a vasculitis. The significant vasculitides that must be considered in this case are Churgg-Strauss syndrome, systemic lupus erythematosus, isolated central nervous system angiitis, and vasculitis secondary to another connective tissue disorder or to

drugs. Although the patient had a history of asthma, there are several factors that mitigate against the diagnosis of Churgg-Strauss syndrome. Firstly it is usually a systemic vasculitis and there is usually severe pulmonary involvement, associated with severe asthma and peripheral eosinophilia. There is often involvement of the peripheral nerves with multiple mononeuropathy as the typical presentation. This woman could very well have had a connective tissue disorder. Entities such as SLE and a vasculitis secondary to another connective tissue disorder could have this patient's condition as an initial presentation. However, a systemic presentation is more common. Since there was no evidence of systemic disease and since a myelopathic presentation is distinctly rare in lupus associated CNS disease, these connective tissue disorders can be excluded. An isolated angiitis restricted to the CNS is possible, however the presentation is usually insidious, rather than acute and devastating, as it was in this case. Finally, the possibility of a vasculitis secondary to drug abuse should be entertained, although there was nothing in the history to suggest this.

The CNS neoplasm that requires consideration and may present in this fashion is CNS lymphoma. This entity is usually found in the elderly and the immunocompromised population, but we are beginning to see an increase in the immunocompetent population as well. CNS lymphoma usually presents however, with focal neurologic findings and involvement of multiple sites including the spinal cord.

Finally, I will give what I believe to be the most likely diagnosis; CNS demyelination including acute multiple sclerosis (MS)-like conditions. The two that are possible explanations include Devic's disease, otherwise known as neuromyelitis optica, and Childer's disease. Devic's disease involves the spinal cord and the optic nerves. It is usually an acute presentation and as many as 50% of patients with this condition can have an influenza-like prodrome. It can have a number of courses including an acute and devastating presentation with death within a few weeks, can spontaneously resolve, or can smoulder along developing into a chronic myelopathic state. Consistent with this entity is the myelopathic presentation. However, we have no evidence to suggest that she had any visual abnormalities. We do know that she had sluggish pupils, but at no time did she ever complain of visual disturbance or blindness, which is sufficiently unusual for this not to be considered further in the differential diagnosis. Another potential explanation of an acute presentation of MS-like symptoms includes Childer's disease. Patients usually present with large enhancing lesions within the cerebrum with significant mass effects. This is typically common in children and it does not resemble anything that we see here.

I suspect the patient experienced a post-infectious demyelination, otherwise known as an acute disseminated encephalomyelitis. It is an acute monophasic illness, that follows symptoms of nonspecific illnesses, such as respiratory tract infections or after vaccinations. Characteristic symptoms include bilateral optic neuritis, confusion, seizures, brainstem abnormalities, myelopathy, and loss of deep tendon reflexes; most of which were experienced by the patient. There are occasionally some systemic findings including systemic leukocytosis and fever. The onset is very rapid and the mortality rate in this condition can be considerable, with values anywhere from 10-30%. The recovery, when it occurs, is not always complete, but the illness is usually monophasic, although can become chronic as well.

Clinical Diagnosis

Acute Disseminated Encephalomyelitis

Dr. Warren P. Mason's Diagnosis

Acute Disseminated Encephalomyelitis

Pathological Discussion

Michael S. Pollanen, Ph.D. (9T9)

Gross examination of the brain and spinal cord revealed no obvious lesions. However, the sections of the spinal cord and brain that were stained with the luxol-fast blue reaction for myelin showed punctate areas of perivascular demyelination (Figure 1 and 2). The distribution correlated very well with the MR findings, as the most severe degree of this abnormality was found at the C7 level. These areas of demyelination were also seen in the basal ganglia, including the thalamus and were found throughout the spinal cord, base of the pons, transverse pontine fibers, and descending long tracts. In the areas of perivascular (chiefly perivenular) demyelination, the vessel and vessel wall were invested with mononuclear inflammatory cells and macrophages (Figure 3). There was astrocytic gliosis in these areas consistent with the relatively protracted course of the illness.

The pathological changes are those of acute disseminated encephalomyelitis. The pathogenesis of this entity is incompletely understood but current research suggests it involves molecular mimicry. This mechanism postulates that a specific T-cell mediated response generated to an oligopeptide sequence of a viral protein subsequently cross reacts with a myelin protein present in the CNS. There is epidemiological and basic scientific evidence to support this hypothesis, including the often antecedent flu-like illness, which was seen in this patient. In terms of the basic scientific basis for molecular mimicry, there have been several interesting studies, which have demonstrated that there is a definite peptide sequence in the myelin basic protein that shares great homology with various capsid proteins of adenovirus, respiratory syncitial virus, influenza, and hepatitis B virus. Theoretically, any antecedent infection with one of these viruses could, in effect, introduce this element of antigenic homology and could result in a T-cell mediated demyelination of the CNS.

Anatomical Diagnosis

Acute Disseminated Encephalomyelitis

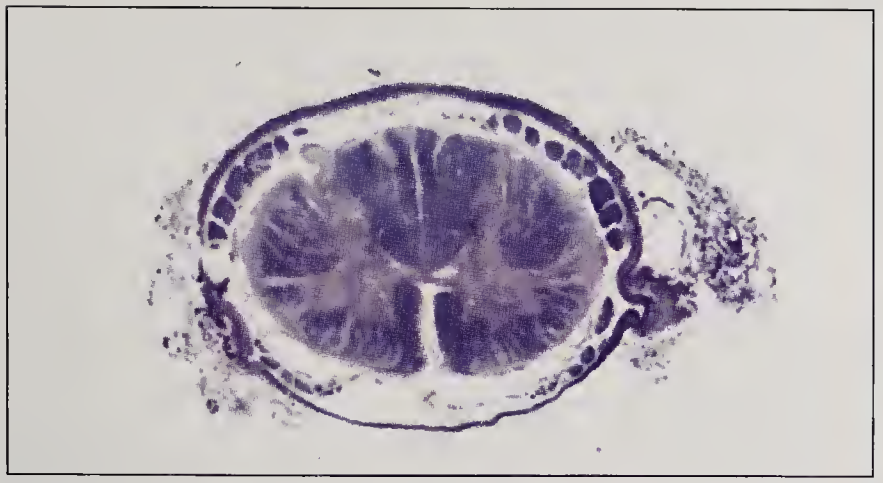


Figure 1: *Horizontal section of spinal cord showing extensive radial-type perivascular demyelination (LFB/HE, 3x).*

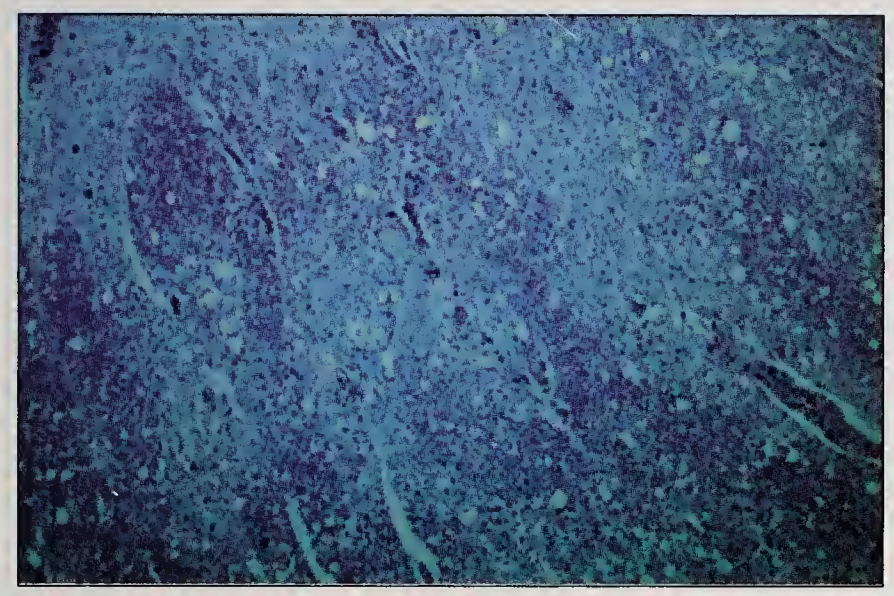


Figure 2: *Patchy and confluent pervivascular demyelination (LFB/HE, 100x).*

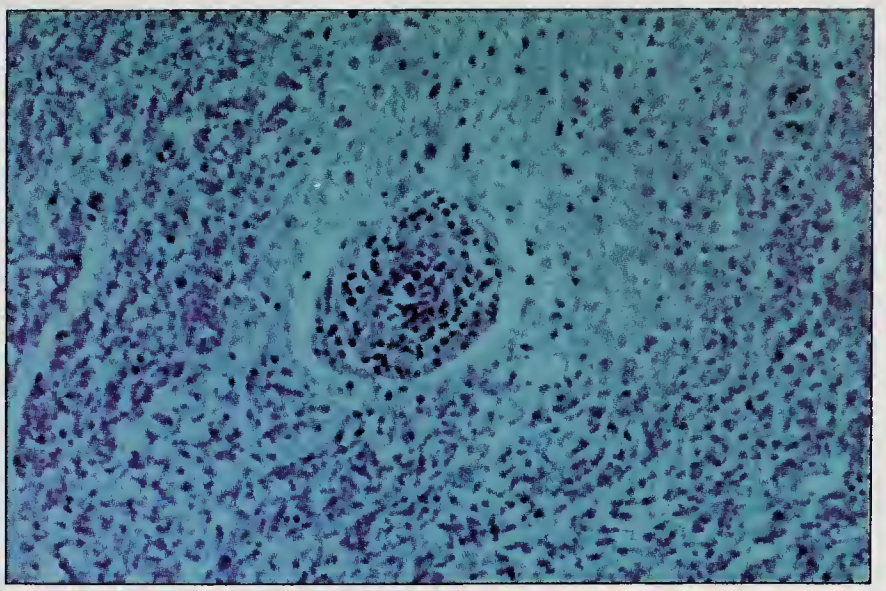
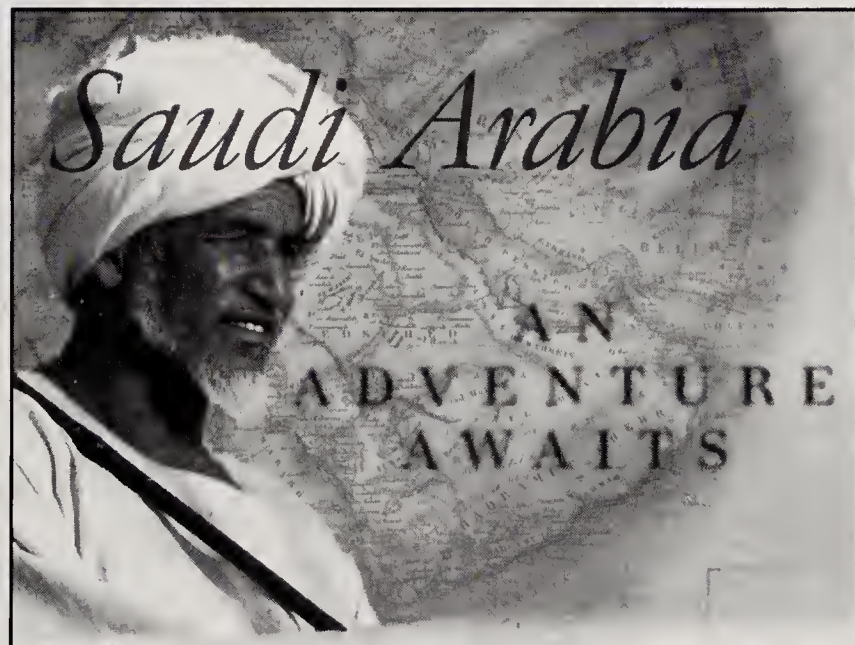


Figure 3: *Perivascular and intramural lymphocytic infiltrate with perivascular demyelination (LFB/HE, 400x).*



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HIV Rounds

Bonnie O'Hayon, B.A. (9T9) and Elizabeth Hait, B.Sc. (9T9)

Case 1

A 35 year old currently healthy male hemophiliac on phenytoin goes to the dentist for a routine cleaning. The dentist notices the following lesions:

What is the most likely diagnosis?

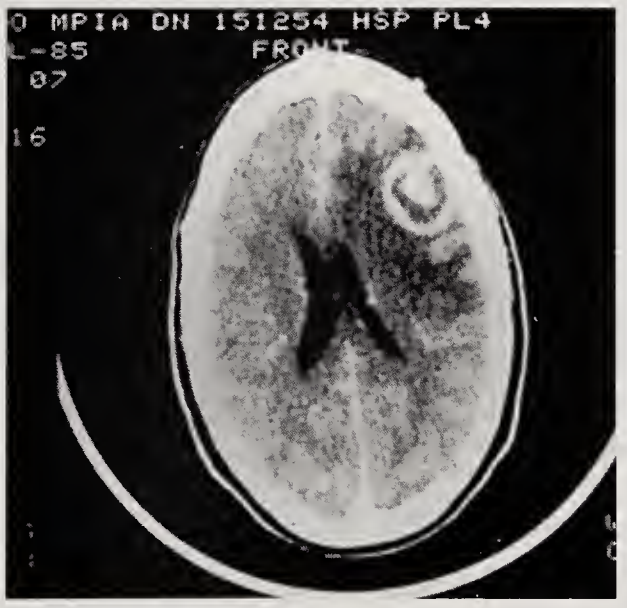
Case 2

A 37 year old sexually active heterosexual male comes to your office after noting the following lesion on his tongue:

What is the differential diagnosis?
Which tests would you order?

Case 3

A 37 year old HIV positive male presents to your office with a two week history of headache, nausea, vomiting, confusion, decreased consciousness, and right sided hemiparesis. His past medical history includes *Pneumocystis carinii* pneumonia, and his CD4 count is 30. His current medications include AZT, 3TC, and aerosolized pentamidine. You see the following results on CT scan:



What is the differential diagnosis?
Which tests would you like to order?

We gratefully acknowledge Dr. David Fletcher of the Immunodeficiency Clinic at The Toronto Hospital for providing the above cases, and Wellcome-Glaxo for providing the slides.

Solutions

Case 1

The most likely diagnosis is *HIV-related Kaposi's Sarcoma* involving most of the hard palate and gingiva. Unlike the "classical" Kaposi's Sarcoma, HIV-related Kaposi's Sarcoma has a variable clinical picture rangng from slow growing single lesions to aggressive, fatal, multicentric visceral disease. Up to 40% of all cases of Kaposi's Sarcoma present in the mouth. It has a characteristic purple red appearance which is usually found on the hard palate. Phenytoin may confuse the clinical picture in this case, as one of its side effects is gingival hyperplasia.

Case 2

Differential diagnosis:

1. HIV-related oral hairy leukoplakia
2. non HIV-related oral hairy leukoplakia
3. oral candidiasis (atypical pattern)

Lab tests: HIV status

This patient was HIV positive and was diagnosed with oral hairy leukoplakia (OHL). This diagnosis is distinguished from candidiasis in that the lesion cannot be removed by scraping. OHL is a result of infection with Epstein-Barr virus. Similar appearances may be seen in candidal leukoplakia, smoker's leukoplakia, and epithelial dysplasia. OHL indicates advancing HIV disease.

Case 3

Differential diagnosis:

1. Toxoplasmosis
2. 1^0 CNS lymphoma

Over 90% of HIV-related focal cerebral lesions are due to toxoplasmosis, primary CNS lymphoma, or progressive multifocal leukoencephalopathy. All these conditions can present in a similar fashion with focal symptoms such as hemiparesis, or with nonspecific symptoms such as confusion, headaches, and fever. Toxoplasmosis, however, is the most common and most readily treatable cause of focal lesions.

Lab tests: Toxoplasma antibodies

This patient was found to positive for Toxoplasma antibodies, and was consequently diagnosed with Toxoplasmosis.

References

Lipman, MCI, Gluck TA, Johnson MA. An Atlas of Differential Diagnosis in HIV Disease. The Parthenon Publishing Group, New York, 1995.

SOFTWARE REVIEW

Reviewed by Stephan Mostowy, M.D. (9T6)
General Surgery Resident, University of Toronto

Introduction

Jeff Singh (9T9)

Nelson's Textbook of Pediatrics, William's Obstetrics and Gynecology, Stedman's Illustrated Medical Dictionary, and *Netter's Atlas of Human Anatomy* – all of these find their way into the backpack of the archetypal second year medical student, Joe Smith. As Joe sets off to his favorite study alcove to continue his pursuit for fluency in the exotic language of differential diagnoses, his pack strains under the gravid weight of its substantial contents. Unfortunately for Joe, however, he is destined to develop a severe musculoskeletal ailment as a result of hauling fifty pounds of texts on his emaciated, sleep-deprived shoulders. Later, while in the care of a rehabilitation therapist, Joe is heard to remark: "If only there was a way to shrink these books into something I could carry . . ."

In last issue's inaugural *Software Review* column, Jordan Weinstein evaluated several commercial diagnostic utilities. He concluded that most of these, despite their considerable cost, were only moderately useful in a clinical setting. One of the key reasons computers have experienced limited success as diagnostic tools is that machines approach clinical problems with a linear, inflexible algorithm, and lack the 'lateral thinking' that distinguishes the human cognitive process.

The human clinical process can be seen to start with the recognition of signs and symptoms, followed by their systematic but loose association to a memorized list of diagnoses. Associations are often made very contextually, based on what one expects to see in a given situation, only to be later confirmed or ruled out. Because of this very 'lateral' style of thinking, one analogy very befitting of physicians is their depiction as 'fuzzy-headed memorizers'. It is this 'fuzziness' which is lacking in current computer diagnostic tools. Despite the use of advanced statistical math and so-called 'fuzzy-logic', programmers have been unable to instill within software either the intuition or the insight which characterizes their sentient creators. In the spirit of a popular medical aphorism: A computer will hear equine hoofbeats, but will never 'sense' that it is about to be trampled by the herd of zebras.

This somewhat disappointing evaluation of current technology then begs the question of whether there is any useful application for computer software in a clinical setting. Despite the failure of modern computer programs to think in abstract forms, the astounding speed and memory capacity of these machines makes them useful resources with which to supplement our own human 'fuzzy' memories. The sheer volume of information easily manipulated by a modern computer is astounding, and it is this potential which must be developed in new medical computer software. One of the most promising applications of this technology is in addressing the wish of the aforementioned medical student – the portability of his cumbersome hardcover textbook. The advent of the CD-ROM, with its exceptional storage capacity, has paved the way for electronic libraries, where volumes of paper and ink are reduced to gleaming discs of ones and zeros. The medical student of the future may jaunt off to the library with full textbooks of medicine, surgery, pathology and pharmacology, all in the form of a laptop and a few CD-ROM's. An even more accessible distribution of these 'computer textbooks' would be achieved over a network, allowing students and clinicians access to them directly from terminals on the wards or at home. Traditionalists may argue that computer books destroy the romantic image of the young medical student studying in the vacillating glow of a candle, but our medical student will certainly argue that a twenty pound edition of *Harrison's Principles of Internal Medicine* is hardly romantic prose!

The success of computer-based textbooks will most likely depend on their ability to provide useful text, visual information, and search engines in a package that is easily accessible at any computer terminal. Regardless of how well the integration of text and visuals is carried out if the information is not immediately accessible to its users, it will never receive more than a casual curiosity on the part of physicians and students. A useful computer interface will allow users to search out information and display it speedily and efficiently, with a limited amount of training or computer literacy. How many times has the average medical student thought: 'I remember reading that somewhere, but where exactly??' – with computer-based search engines, this information is only a few keystrokes away. Entering a few words will produce a list of relevant chapter and electronic page headings. The development of good computer textbook interfaces will not only make information more portable, but also make it more accessible.

As a first look into the world of computer-based textbooks, Dr. Stephan Mostowy, a general surgery resident, reviews the new CD-ROM edition of the *Oxford Textbook of Surgery,* specifically evaluating not only the format and content of the CD-ROM book, but comparing the benefits and disadvantages of both the electronic and 'traditional' mediums.

Oxford Textbook of Surgery on Compact Disc

Edited by Peter J. Morris and Ronald A. Malt
Oxford University Press and AND Electronic Publishing B.V.
Rotterdam, 1995

Cost:	Single user:	$570.95
	2-5 Network:	$1620.00
	6+ Network:	$3200.00

The *Oxford Textbook of Surgery* (OTS) has been a landmark reference resource. The *Oxford Textbook of Surgery* aims to present a picture of surgery in its totality by bringing together the experience of surgical practice from two major clinical schools – Oxford University Clinical School and Massachusetts General Hospital of Harvard Medical School. A recent CD-ROM version was produced with the goal of accessing the information of the printed book with speed, precision, and flexibility using software. As will be further discussed, this format of the landmark surgery reference has both advantages and disadvantages over the traditional paper-based version.

The *OTS* tries to unify all the branches of surgery under one roof in a comprehensive textbook of surgery in this age of increasing specialization. By approaching surgery from a practical point of view, it has attempted to cover most aspects of general surgery as well as giving a solid overview of the various surgical specialties ranging from cardiac to plastic surgery. The broad range of topics that are presented allows a beginner to develop an approach to a clinical surgical problem, making this textbook an educational resource to all students regardless of their level of expertise.

The OTS contains substantial information about the diseases which require surgery, the indications for the operation, and the possible adverse consequences of operative therapy. Practical and technical questions commonly faced by surgeons before entering the operating room or performing bedside procedures (e.g., chest tube insertion) are also addressed. Most of the clinical chapters provide information on epidemiology, surgical anatomy, physiology, pathogensis, clinical, and operative aspects of the relevant material. To address issues of academic surgical practice there are useful sections on "Design of controlled clinical trials" and "Molecular biology and clinical practice". In addition, each chapter is accompanied by a bibliography with useful references for those readers requiring more detailed or up-to-the-minute information.

The CD-ROM version contains all the basic and clinical information found in the printed textbook. The benefit of this format is that the *Oxford Textbook of Surgery* can be accessed with speed and flexibility in an environment that allows one to:

- search for any word or combination of words anywhere in the text, tables, figure captions, and references
- use any of the four different search methods: free text, table of contents, index, and authors
- use a thesaurus, wildcards, and Boolean operators to make the search more flexible
- print our any part of the text or copy it to the clipboard
- adjust the font size and customize the proportion of the screen
- scan through a section's figures at reduced size before viewing the chosen illustrations at full size
- use bookmarks at any point in the text – an easy means of returning to the same spot later

One of the positive features of the CD-ROM is that this format retains the logical flow of the textbook which emphasizes a pragmatic approach to the problems surgeons encounter. The text is made alive and attractive by widespread use of colour for illustrations and tables. Enhancing the text, the tables and figures provide a method of rapid information gathering.

Advantages of the CD-ROM version are that it allows rapid searching options and provides instant figures and diagrams. The table of contents allows the user to keep track of what sections one has read and thereby give quick access to previously researched topics. It is formatted for someone at every level to gain something. Another asset of the CD-ROM is the fact that it is compact. The program can be accessed anywhere there is computer linkage, potentially on the scene – thereby avoiding carrying a textbook or trekking to the library.

Using a mouse to browse through text, the CD-ROM is more interactive than the book. A positive cycle is created: more use of the program makes searching easier, and thus more can be learned. The computer explores one's inquiries and tries to find a match providing a more extensive search compared to just looking in the index of a book. The CD-ROM has many advantages over the textbook form except that the textbook is much more pleasant to read compared to the monitor screen.

However, it provides the option of printing highlighted sections and thus one can read from paper. Other shortfalls of the CD-ROM version stem from its failing to fully capitalize on the interaction between user and program. The program is essentially a textbook on the computer screen, and thus creates an extremely static environment. The tables, pictures, and diagrams are well laid out yet there is no case-based interaction. A dynamic interaction may be a more effective use of the computer in trying to teach surgery. A format that applies principles of surgery and adapts to the probing mind of the user has not been created in this program. It may not achieve the task of converting a hardened textbook reader to using the electronic medium.

An important issue for students and faculties is the cost for the CD-ROM version. For a single user, it is twice the cost of the textbook itself. It seems difficult to justify purchasing this program for a home computer. It seems that it is more suited for purchase by academic centres. Perhaps these institutions may find the search engine worth the cost.

This program would be ideal to have on a surgical floor, which a medical student, clinical clerk, or resident could access immediately. This would ensure that the person can follow-up on a clinical question at the site of an encountered situation, thereby learning at the highest level of enthusiasm rather than having to wait until getting to a library to satisfy their curiosity. On the surgical floors, students would be able to challenge themselves intellectually.

This CD-ROM is definitely a solid beginning for future editions employing the powers of the computer age and multimedia methods to educate and inform. Perhaps this multimedia approach will prove to be more stimulating for students of surgery, driving them to ask more questions and seek more answers in this interactive format. Students may fnd this helpful and easy because of the high quality of its presentation, organization, and content. While reviewing this program, I looked forward to settling down in the evening and digesting a few topics. It was exciting to explore my surgical interests with this text. As with textbooks, this CD-ROM is not to be read from "cover to cover", but rather should be seen as a portal of entry into the field of surgery for the learning mind.

Computers have great potential as information resources in all medical fields, immediately placing volumes of medical knowledge at the fingertips of any clerk, resident, or physician. It is clear that the strength of computer software at its current state of evolution is not in diagnostic problem solving but in information handling and provision. In a clinical setting, computer applications such as the *Oxford Textbook of Surgery on CD* will be of great use as resource or adjunct to clinical learning. In essence, to return to our poor second-year medical student, he can now search out and read about hoofbeats from any terminal in the hospital, but is left on his own to distinguish the zebras from the horses.

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A Design for the Future of Health Care

Dr. Larry Bryan

Oxford University Press

$20.00

A Design for the Future of Health Care is a brief examination of various health care models around the world and their relevance to the health care revolution in Canada. It highlights the difficulties faced by our own health care system as well as those faced by other systems in industrialized nations and offers potential directions for the future.

Models of health care delivery and funding are undergoing rapid change throughout Canada and around the world. The driving pressures which have resulted in this movement are the increasing fiscal restraint of governments and the fact that the progress in medical technology is outpacing the ability of various systems to adapt to it. Thus, health care systems are being closely examined for their ability to provide the best possible service at the lowest possible cost. The methods being used to achieve this goal, internationally and particularly in the United States, include not only the job losses and pay cuts usually associated with corporate restructuring, but also research into which treatment modalities are truly effective and which are no longer required. The relevance of such restructuring in other nations to the Canadian system is demonstrated clearly by the author and is substantiated with current data comparing cost effectiveness to treatment efficacy. This approach is highly informative to the reader who requires an insight into the restructuring process, as the author attempts to provide the reasoning used by the groups that are implementing the reforms.

The author also uses descriptions that students and practitioners who are not actively involved in health care reform can understand. The content, therefore, provides a good basis for those in the medical community who simply wish to better comprehend what is occurring around them. For those who are already knowledgeable in this area, the book in unlikely to offer much new information and may not be worthwhile.

Priced at roughly $20 and approximately 150 pages in length, this book offers both affordability and brevity. However, it must be understood that the opinions of the author are just that, one person's opinions, and should not be taken as the definitive directions that health care will take.

I recommend this book as a good source of general information on the global trends in health care and the possible effects of those trends on the Canadian system. For students specifically, an understanding of these trends is important, as students will be most heavily affected by them. Most will find a brief section regarding which specialties will be oversupplied in the future particularly notable. This is where the author's use of concrete examples as opposed to theoretical jargon is most relevant to students in their first few years of medical training. Specialties which are currently experiencing difficulties in other countries with regards to the issues of employment, renumeration and location in hierarchies are identified. The author describes the reasons for these difficulties and, based on this reasoning, predicts the future scenarios that other specialties will also face. This section alone makes the book of some value to those who are uncertain of the careers they wish to choose.

The author's target audience appears to encompass anyone who is working or training in the health care field, whose knowledge of health care restructuring is limited. Although occasionally confusing due to the variety of international health care models examined, the brief and concrete format works well in elucidating the mysteries surrounding the process of reform. However, the author examines the issues from the perspective of improving health care and rarely takes a pro-physician stance. In fact, some may find a few statements, regarding a lack of altruism and resistance to change among physicians, particularly troublesome. However, for those who are willing to accept criticism, warranted or not, in exchange for knowledge, this book will be worthwhile.

Prince Aujla, B.Sc. (0T0)

HIV, AIDS & Childbearing Public Policy, Private Lives

Ruth R. Faden and Nancy E. Klass (editors)

Oxford University Press, 1996

$57.50

In the United States, the highest incidence of HIV infection in women is among women of reproductive age (22 to 44). The majority of these cases are linked to injection drug use, either by the women themselves or their sexual partners. Many of these women face marginalization due to poverty, race, or drug abuse, in addition to the burden of a stigmatising and ultimately a fatal medical condition. Viewed by many as having attributes undesirable for childbearing and motherhood, these women face a society that would like to see restrictions, voluntary and involuntary, placed on their reproductive capability. *HIV, AIDS & Childbearing,* edited by Ruth Faden and Nancy Klass, is an attempt to elucidate and analyse the moral, legal, medical, and public policy issues regarding the rights of HIV infected women to have children.

The book, written in five parts, has numerous contributors. Part I is devoted to medical and public health issues. The information is primarily epidemiological and represents a simple overview of a wide variety of topics including: the

clinical course of HIV infection; vertical transmission; psychosocial issues for children born to HIV-infected mothers; and access to health services. Legal issues are covered in Part II, with particular emphasis on the legality of state intervention and tort liability. Of interest to the clinician, there is a section on liability issues for health-care providers, with an emphasis in the area of reproductive counselling. Part III, on ethical and social issues, presents very detailed analyses of the ethical principles of counselling, the moral right to have children, and moral multiculturalism. Part IV veers away from the theoretical. In *Voices From The Community,* the issues are brought to life when the reader is presented with the words and experiences of HIV-infected women. There is also a chapter on the practices and opinions of health care providers, but the generalizability of these ideas should be carefully assessed as they are based on a very small sample. The book is concluded with Part V, a presentation of public policy and clinical practice recommendations and guidelines. The guidelines geared towards clinicians are limited, with the focus being on public policy. However, in giving their recommendations the authors provide a good summary of the issues covered in several of the preceding parts, with references to the relevant chapters.

Of note from a Canadian or international perspective, is that this book is based solely on the American experience with HIV and AIDS. Unfortunately, the reader is left to surmise on his or her own how the issue of HIV and childbearing may be viewed in countries differing from the United States with respect to the demographics of the HIV/AIDS epidemic, social and cultural values around childbearing, legal rights of the individual, and medical and pharmacological resources.

Overall, this group of contributors present very detailed arguments, legal, moral, and philosophical, both for and against the rights of HIV-infected women to have children. This is both a strength and a weakness depending on the target audience. For medical students or clinicians who simply want to increase their awareness of the issues, the last two chapters provide a good focus (and would require a trip to the library rather than the bookstore). However, for the social scientist, ethicist, medical philosopher, or clinician who desires to understand the debate from a theoretical perspective, this book is rich in detail and has a lot to offer.

Colette Rutherford, MHSc, (9T9)

Health Promotion - Models and Values, 2nd ed.

R.S. Downie, C. Tannahill, A. Tannahill

Oxford University Press, 1996

$42.95

Health Promotion: Models and Values makes an outstanding effort to define clearly a comprehensive model of health which encompasses the realms of health education, prevention, and protection. In addition, the second part of the book goes on to define attitudes and values and to illustrate how they relate to health and how they can affect the implementation of these models and thus their effectiveness. This book successfully emphasizes, through clarification and discussion, the necessity of viewing health as a multidimensional concept. It broadens the traditional viewpoint of health as a lack of illness to include social and psychological considerations in addition to physical ones.

The book is divided into two parts. The first is mainly theoretical and includes a detailed description of health viewed from a traditional stance and then a more modern view encompassing various psychosocial aspects. Then, the need for positive health education aimed at changing the attitudes and behaviors of the general public as well as those of policy makers is discussed, along with various approaches that can be used to most effectively communicate ideas and meet that need. A comprehensive model of health promotion is presented with three naturally overlapping domains of health education, health promotion, and health prevention. This model is clearly defined and an arena-based approach to achieving its objectives is well-argued. Next, the real need for program evaluation is demonstrated with emphasis on the assessing not only the achievement of aims, but also that of process, which includes use of resources and methods used. Finally, real case examples of the health promotion model earlier defined are presented providing an excellent sense of applicability and value.

The second part of the book is devoted to values, their origin and their manipulation. Attitudes are extensively considered and presented as changeable entities that are reflected in feelings and behaviors. Then, clear strategies to influence attitudes to increase positive health behaviors are presented. A very strong and beneficial argument is made to counteract frequent objections which are leveled against a holistic approach to health. Finally, the value basis of this holistic health view is defined with respect to a fundamental personal value for autonomy and societal values of justice. This second section is fairly philosophical and quite interesting. It stimulates thought and reinforces personal support of health promotion.

The content of this book is extremely topical and presented in an straight-forward and understandable manner. The writing style of the authors is clear and concise. The text is well-supported with references and the author's powerful grasp of this topic is quite evident. They present various definitions and extensively discuss different viewpoints finally arguing the relevancy of one particular perspective. Also this book often progresses from a very basic descriptive level of models or values to an in-depth and high-level discussion, which at times assumes background knowledge. Hence, this book can serve as a useful resource for both the novice and the authority in the field of health promotion.

Raveen S. Pal, M.Sc. (0T0)

Respiratory Physiology: People and Ideas

Edited by John B. West

Oxford University Press, 1996

$121.95

Respiratory Physiology: People and Ideas is the fifth installment of the People and Ideas series produced by the

American Physiological Society (APS). This is a recent series of books published by the APS in order to explicate how physiological theory and ideas developed during the twentieth century. In the words of John B. West (editor), "...the thrust of the books is to bring the history of each topic close to the present day."

This volume is neatly broken down into comprehensive sections devoted to morphology, gas exchange and blood flow, mechanics, control of ventilation, and comparative physiology, with each section containing chapters contributed by fifteen different experts in respiratory physiology. Each chapter defines the scope of its topic and begins with an historical perspective of the origin of research into that particular area. Important landmarks of discovery and the individuals responsible for them are duly noted. In addition, at the end of each chapter there lies an extensive list of references to the historical key points as well as more recent studies.

Although every chapter is laden with different areas of expertise, the variability in the content lends to a lack of continuity throughout the book. There are some purely instructional and physiologically based chapters, like the one dedicated to Rhythm Generation, with the bulk of the information provided by intense neurophysiology and animal experimentation. Others, such as the section devoted to Gas Exchange and Blood Flow, are far more historical in their nature and focus purely on the people involved with the work, as opposed to the work itself.

For the reader with even a limited background in respiratory physiology the concepts explored in this book are easily understandable and the historical insights are quite interesting. However, for those readers with a broader base of knowledge, including medical students, the concepts prove to be at times simplistic and at others, beyond the focus of medical practice.

The material presented is purely physiologically research based, and although this is not a bad thing, it lacks the clinical correlations and underlying pathophysiological mechanisms medical students require. This book is clearly not geared towards the medical student market, and with a price tag of $121.95, it insures that it will remain that way.

Deep Chatha, M.Sc. (9T9)

Interviewing and Patient Care, 4th ed.

Allen J. Enelow, Douglas L. Forde, and Kenneth Brummel-Smith

Oxford University Press Canada

$27.50

The importance of the interview in medicine cannot be overemphasized. It is commonly suggested, independant to other aspects of the clinical encounter, that the interview can lead to a diagnosis in approximately three quarters of patients. The interview is also the first step in the establishment of a good relationship with the patient, which is necessary for providing care in an effective and cooperative manner. Unfortunately however, learning the interview is an exercise that plagues all health care providers because it is a skill that requires continuous practice, and perfection. *Interviewing and Patient Care* is a book that can equip the beginner with the tools that are needed to enter the hospital and begin patient contact. It is also an appropriate source for people who have some interview experience, so that they can reflect on their own interviewing styles, and identify areas that need improvement.

The book begins with an introduction to basic interviewing, and then moves on to discuss the medical history. The book next focuses on areas that might pose particular problems to the interviewer, including difficult patients, and uncomfortable situations. An entire chapter is devoted to interviewing the elderly. This chapter describes how to optimize communication with a person that might have some degree of sensory impairment, and also discusses some of the problems that are more prevalent in the elderly. A similar chapter on interviewing children is also included.

The authors do much more than lecture on the skills needed to interview by providing context through many interesting anecdotes. These examples were gathered from students learning how to interview in a hospital setting. Unlike other bookds written on this subject, *Interviewing and Patient Care* takes into account that you are capable of communication skills that were learned at a grade one level, the book builds on pre-existing skill to provide you with the tools that are needed for successful communication in the specific realm of health care delivery. As a second year medical student with some interview experience, I found the examples in the book especially entertaining since they often described student errors that sounded remarkably familiar.

This is the fourth edition of *Interviewing and Patient Care.* Many new additions have been included in this latest version. These include the chapter on how to take a proper medical history from children, as well as a chapter on breaking bad news. In addition, other chapters have been revised to include information on issues that are becoming increasingly prevalent in modern society such as same sex issues, and interviewing patients from other countries of origin.

Although the book is an American publication, the tools it teaches are universal, and aside from the occasional mention of HMO's, all the information applies equally well to Canadian readers. I thoroughly enjoyed the book because it summarized many of the skills that were taught in medical school, and was able to remind me of some of the techniques I had developed with respect to interviewing. I would recommend it to anyone who is interested in learning more about interviewing, irrespective of profession, or previous interview experience.

Kevin Sanders, B.Sc. (9T9)

Instructions to Authors 1996-97

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The Editors
University of Toronto Medical Journal
Room 2141, Medical Society Office
Medical Sciences Building
Toronto, Ontario M5S 1A8

A **cover letter** signed by all authors must state that the manuscript has never been published by any other journal and is not presently under consideration for publication. It should also explain the purpose of the paper and its intended readership.

We require the original manuscript with CAMERA-READY photographs, figures, line drawings, and graphs along with three additional complete copies.

Pages of the manuscripts must be numbered and typed, double-spaced, on paper approximately 22 x 28 cm. Submissions should not exceed a maximum of 4000 words and shorter papers are preferred. The title page should include the **author's names, graduating year** (if from U of T), **degrees,** and **appointments.** To facilitate the peer review process, this information must not appear on any other part of the manuscript.

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Reinders FX, Chalin C, and Meier HMR. Alzheimer's disease: Understanding the patient and caregiver. UTMJ 1993; 70(2): 16-20.

For further details, see CMAJ 1985;133:443-448.

Tables - Tables should have a short title, and be numbered and referred to in the text. Column headings and descriptive matter in tables should be brief. Vertical rules should not be used.

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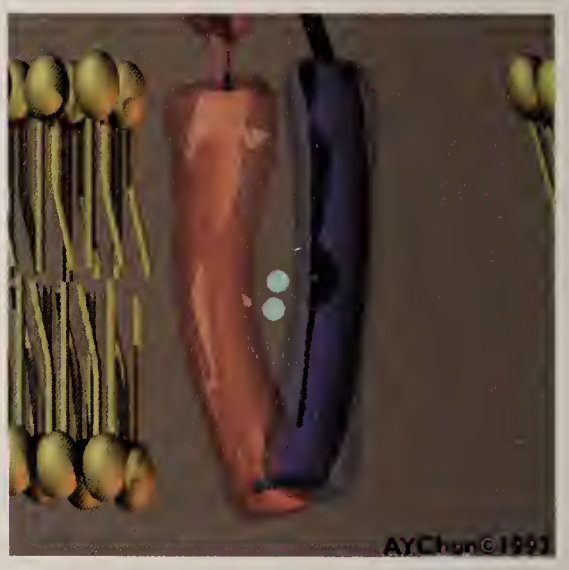
Still images from the animation of the structure and function of the sarcoplasmic reticular calcium ATPase enzyme of muscle

#1.

#2.

#3.



Front view of the sarcoplasmic reticular calcium ATPase before the calcium-binding event; phosphorylation of the enzyme has not occurred.
#1. Phosphorylation occurs, triggering movement of secondary structures of enzyme.
#2. Movement is transferred through "neck" of enzyme.
#3. Movement reaches transmembrane region, trapping calcium in enzyme.
(Light green molecule=ATP; light blue molecules=calcium.)

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